UNIV. OF
TORONTO
LIBRARY

BINDING LIST SEP 1 5 1923

Med
A
7739
I

AMERICAN JOURNAL
OF
DISEASES OF CHILDREN

EDITORIAL BOARD
H. F. HELMHOLZ, Rochester, Minn.
L. EMMETT HOLT, New York City
DAVID M COWIE, Ann Arbor, Mich.
FRITZ B. TALBOT, Boston
W. McKIM MARRIOTT, St. Louis
JOHN HOWLAND, Baltimore

VOLUME 25
1923

184938
27.10.23

PUBLISHERS
AMERICAN MEDICAL ASSOCIATION
CHICAGO, ILL.

RJ
1
A5
v.25
cop.2

CONTENTS OF VOLUME 25

JANUARY, 1923. NUMBER 1

PAGE

Physiology of Exercise in Children. Part 1. A Study of Normal Children of School Age. Max Seham, M.D., and Grete Egerer-Seham, Ph.D., Minneapolis ... 1
Celiac Disease. Rood Taylor, M.D., Minneapolis ... 46
The Treatment of Flat Warts by the Internal Administration of Mercury. Howard Fox, M.D., New York ... 55
Comparison of Diphtheria Immunity in the Mother and in the New-Born. H. O. Ruh, M.D., and J. E. McClelland, M.D., Cleveland ... 59
Chemical Studies of the Blood of Mother and Fetus. Marion G. Howe and Maurice H. Givens, Pittsburgh ... 63
The Colloidal Gold Reaction in Acute Poliomyelitis. Joseph C. Regan, M.D.; Abraham Litvak, M.D., and Catherine Regan, M.D., New York ... 76

FEBRUARY, 1923. NUMBER 2

The Influence of Growth on the Basal Metabolism of Children. G. B. Fleming, M.D., Glasgow, Scotland ... 85
Neuropsychiatric Sequelae of Acute Epidemic Encephalitis in Children. Franklin G. Ebaugh, M.D., Philadelphia ... 89
Acute Hemorrhagic Encephalitis: Report of Case Following Scarlet Fever. John A. Toomey, M.D.; Leon H. Dembo, M.D., and Guthrie McConnell, M.D., Cleveland ... 98
Intraperitoneal Transfusion with Citrated Blood: An Experimental Study. David M. Siperstein, M.D., Minneapolis, and J. Martin Sansby, M.D., St. Paul ... 107
Congenital Malaria: Report of a Case in Colorado. R. P. Forbes, M.D., Denver ... 130
The Excretion of Foreign Protein in Human Milk. Harold C. Stuart, M.D., Boston ... 135
Oxygen Therapy in Premature Babies with Anoxemia. Harry Bakwin, M.D., New York ... 157
Toxemia of Severe Superficial Burns in Children. Bruce Robertson, M.B. (Tor.), and Gladys Boyd, M.D., Toronto, Canada ... 163
Progress in Pediatrics:
  A Review of the Literature on the Blood and Blood Diseases of Infants and Children for the Last Four Years (1918-1921). Louis Webb Hill, M.D., Boston ... 168

MARCH, 1923. NUMBER 3

The Value of Basal Metabolism in the Diagnosis and Treatment of Cretinism. Fritz B. Talbot, M.D., and Margaret E. Moriarty, Boston ... 185
The Bacteriology of the Urine in Acute Nephritis in Children. Lewis Webb Hill, M.D.; Emily F. Hunt, A.M., and Elsie W. Brown, A.B., Boston ... 198
Intraperitoneal Transfusion with Citrated Blood: A Clinical Study. David M. Siperstein, M.D., Minneapolis ... 202
Polycystic Disease of the Kidneys: Report of Case in an Infant. Abraham Tow, M.D., New York ... 222
Lead Poisoning in Infancy. L. Emmett Holt, Jr., M.D., Baltimore ... 299
Types of Organism Found in a Series of Tuberculous Children. J. Keith Gordon, M.D., and Elsie W. Brown, B.Sc., Boston ... 234
Calcium Absorption in Children on a Diet Low in Fat. L. Emmett Holt, M.D., and Helen L. Fales, New York ... 247

CONTENTS OF VOLUME 25

APRIL, 1923. NUMBER 4

PAGE

Brain Tumors in Young Children. A Clinical and Pathologic Study. Martha Wollstein, M.D., and Frederic H. Bartlett, M.D., New York 257

The Characteristics of the Cerebrospinal Fluid in Postdiphtheric Paralysis. Joseph C. Regan, M.D.; Catherine Regan, M.D., and Brickhouse Wilson, M.D., Brooklyn 284

Transfusion Through the Umbilical Vein in Hemorrhage of the New-Born. Report of a Case. J. Buren Sidbury, A.M., M.D., Wilmington, N. C. 290

The Causes of Absence in a Boys' School. C. H. Sanford, M.D., Concord, N. H. 297

The Saliva of the Nursling. A. Hymanson, M.D., New York, and Heinrich Davidsohn, M.D., Berlin 302

A Bacteriologic Study of Acute Diarrheas in Young Children. Martha Wollstein, M.D., New York 310

A Statistical Analysis of the Causes of Palpable Lymph Glands in the New-Born. Louis Dunn, M.D., and Halbert L. Dunn, M.A., M.D., Minneapolis 319

Book Reviews 338

MAY, 1923. NUMBER 5

A Critique of the Pirquet Feeding System with Special Reference to Its Underlying Principles. Harold K. Faber, M.D., San Francisco 339

Mongolism in One of Twins and the Etiology of Mongolism. T. Halbertsma, M.D., Haarlem, Holland 350

Ulcerative Stomatitis and Its Treatment by the Intravenous Injection of Arsenic. Edward A. Morgan, M.B., Toronto 354

The Treatment of Vascular Nevi with Radium. R. H. Rulison, M.D., and Stafford McLean, M.D., New York 359

Atresia of the Duodenum and Right Internal Hernia: Report of a Case. John J. Morton, M.D., New Haven, Conn. 371

Myelogenous Chloroma: Report of Case with Necropsy. Nathan Chandler Foot, M.D., and Gwendolyn Jones, M.D., Cincinnati 379

The Schick Test Performed on More Than 150,000 Children in Public and Parochial Schools in New York (Manhattan and the Bronx). Abraham Zingher, M.D., New York 392

The Water Content of Infants' Blood During Periods of Rapid Increase in Weight. Harry Bakwin, M. D., New York 406

Book Reviews 411

JUNE, 1923. NUMBER 6

The Importance of Colostrum to the New-Born Infant. Ann Kuttner, Ph.D., and Bret Ratner, M.D., New York 413

A Case of Cerebral Cyst in an Infant. H. G. Jacobi, M.D., New York 435

Malignant Hypernephroma in Children. Lynne Hoag, M.D., Ann Arbor, Mich. 441

Studies of Tetany. I. The Effect of Calcium Chlorid Ingestion on the Acid-Base Metabolism of Infants. J. L. Gamble, M.D., Boston; G. S. Ross, M.D., Montreal, and F. F. Tisdall, M.D., Toronto 455

Studies of Tetany. II. The Effect of Ingestion of Hydrochloric Acid Producing Substances on the Acid-Base Metabolism of an Infant and the Probable Manner of Their Action in the Treatment of Tetany. J. L. Gamble, M.D., Boston, and G. S. Ross, M.D., Montreal 470

The Effect of the Spray Process of Drying on the Vitamin C Content of Milk: A Preliminary Report. George Cavanaugh, B.S.; R. Adams Dutcher, M.S., and James S. Hall, Ithaca, N. Y. 498

American Journal of Diseases of Children

Vol. 25 JANUARY, 1923 No. 1

PHYSIOLOGY OF EXERCISE IN CHILDHOOD

PART 1. A STUDY OF NORMAL CHILDREN OF SCHOOL AGE *

MAX SEHAM, M.D., AND GRETE EGERER-SEHAM, Ph.D.
MINNEAPOLIS

INTRODUCTION

Muscular exercise is one of the first instincts of the human organism. The stretching out and manipulating of the legs and arms is among the earliest reflexes of the new-born. Because muscular exercise is so constantly a part of daily life and so obvious in its practical application, medical practitioners have come to regard its physiology as an established truth, into the true nature of which search is unnecessary. The subject of muscular exercise should be of more than mere academic interest to the pediatrist. A clearer understanding of the physiology of this subject and the establishment and effective application of physiologic standards will lead to a higher degree of efficiency of our school children and will increase our knowledge of diagnosis in children from a functional point of view. Only on the basis of quantitative scientific investigation of the physical capacity of normal children of all ages and of the effect of muscular activity of all types on the circulatory system, can we ever hope adequately to provide for physical education and successfully to cope with the prevention of those diseases in children which are dependent on muscular deficiency.

When we recall that 30 per cent. of our soldiers were physically defective; when we learn from a survey of 20,000 New York school children that from 20 to 30 per cent. have spinal curvature, that about 10 per cent. have other postural defects, that from 6 to 30 per cent. suffer from malnutrition, that 5 per cent. exhibit other signs of muscular insufficiency; when we understand that in a survey of a public school in Minneapolis, 8 per cent. of the children were found to be asthenic, the analogue of soldiers with "effort syndrome"; when we bear in mind that all of these conditions are preventable and curable by general physical education and properly administered corrective exercises, we must acknowledge the practical importance of a fundamental study of the effect of various types of work and play under all obtaining conditions on the circulatory system of the child.

---

* Received for Publication Aug. 2, 1922.

* From the Department of Pediatrics, University of Minnesota Medical School.

It may be in place to mention here that the quantitative determination of the mechanical output of the human engine is not as easy as that of a steam engine, for example. In the latter case all factors involved can be measured accurately. The human engine, however, can draw on its reserve power, which varies with different persons, depending largely on a factor ruled by the central nervous system. No method has yet and probably never will be found for its determination. Therefore, the results of a study of the quantity of human muscular output must be relative. This applies also to the data recorded in this paper.

Physiology of Exercise.—In normal children exercise is accompanied by an increase in the pulse rate and the systolic blood pressure. At the very thought of exercise, impulses pass to the inhibitory centers, lessening the vagus tone, and thereby quickening the circulatory reactions.

Immediately after exercise has begun, the curves of the pulse rate and blood pressure ascend abruptly, reaching their apices within about five minutes, and then forming a plateau with slight remissions until the end of exercise.

The contraction of the muscles employed forces the venous blood from the extremities into the great veins, thus causing an overfilling of the right heart; the venous pressure is increased; this, in turn, increases the pulse rate.[1]

Passage of larger amounts of epinephrin into the blood, rise of body temperature, irradiation of impulses from the respiratory center to the vagus nerve, increased H-ion concentration of the blood with its effect on the vagus center, vasoconstriction in the splanchic area and the dilatation of the vessels of the skin and muscles, are other factors influencing the increase of the pulse rate and the blood pressure during exercise.

Work of Previous Authors.—Up to 1920 all investigations of the effect of physical exercise on the circulatory reactions were limited to adults. Though considerable in number they do not permit quantitative conclusions. A comparison of the results is almost impossible, because in many instances neither the type of work (strength or endurance tests) nor the quantity of work were recorded. The outline of the work in which the authors considered at least one of the two factors mentioned above is presented in Table 1. It can be seen that no two investigators employed uniform technic; nor can quantitative standards be established from any of the results obtained because of the small number of subjects studied.

Previous to 1900, the effect of exercise had been studied only on the pulse rate. McCurdy [2] was one of the first in this country to make a systematic study of the effect of lifting heavy weights (strength test) on the pulse as well as on the systolic blood pressure, in a group of trained adults. He found, that the pulse and blood pressure rose rapidly during exercise to fall very quickly to normal after cessation of work, the pulse within sixty seconds, the blood pressure in from two to three minutes. Gruenbaum and Amson,[3] working independently of McCurdy, observed that any form of exercise increased the pulse rate; and that the rise persisted throughout the exercise. The increase varied with the kind, speed and duration of the exercise and was influenced by the training of the subject.

---

[1] Bainbridge, F. A.: The Physiology of Muscular Exercise, New York Longmans, Green and Co., 1915, pp. 3 and 187.

[2] McCurdy, J. H.: The Effect of Maximum Muscular Effort on Blood Pressure, Am. J. Physiol. **5**:95, 1901; Am. Physical Educat. Rev. **14**:493, 1909.

Masing[4] subjected adults of different ages to the same kind of exercise. He concluded:

> Practically all types of work increase the systolic blood pressure in all ages; the rise depends upon the amount and duration of work. The will power greatly influences the rise of pressure in young people. In younger adults the blood pressure remains at about the maximum level throughout the exercise while in older people the initial rise is followed by a fall. Equal quantities of work produce a more rapid and higher rise in the aged than in the young. The increase of blood pressure decreases with repetition of exercise.

Bowen[5] determined the effect of bicycling on the pulse rate and blood pressure during and after exercise. Unfortunately, he did not record the amount of work performed nor the figures obtained. He arrived at the following general conclusions:

> After moderate amounts of work the blood pressure falls rapidly to reach the normal level within a few minutes, contrary to the pulse which after an initial sharp fall remains above normal for a considerable length of time, even for as long as an hour. The maximum rise of peripheral pressure is obtained during the first five to ten minutes of exercise, continuation of exercise causes a slight decrease, and cessation a more pronounced drop to normal or subnormal.

Lowsley,[6] inquired into the effect of moderate and severe exercise on the pulse rate as well as the systolic and diastolic pressures in trained athletes. His findings were: Moderate forms of exercise, as the playing of games for short periods increase the blood pressure not more than ten mms., and the pulse rate from 16 to 36 beats per minute. At the cessation of exercise, the blood pressure and pulse rate fall, the former usually below normal, the latter remaining above normal for a prolonged and variable period. Strenuous exercise for short periods

---

[3] Gruenbaum, R., and Amson, A.: Einfluss von Bewegung auf die Pulsefrequenz., Wien. med. Presse. **42**:2161, 1901.

[4] Masing, E.: Ueber das Verhalten des Blutdrucks des jungen und des bejahrten Menschen bei Muskelarbeit, Deutsch. Arch. f. klin. Med. **74**:253, 1902.

[5] Bowen, W. P.: Changes in Heart Rate, Blood Pressure, and Duration of Systole Resulting from Bicycling, Am. Physical Educat. Rev. **8**:8, 232, 1903; Am. J. Physiol. **11**:59, 1904.

[6] Lowsley, O.: Effect of Exercise on Pulse and Blood Pressure, J. Physiol. **27**:446, 1915.

TABLE 1.—WORK OF PREVIOUS AUTHORS

Author	Number of Cases	Disease	Type of Exercise	Amount of Work	Normal Pulse	Normal Blood Pressure	During Exercise						After Exercise									Remarks
							Pulse Increase		Systolic Increase		Diastolic Increase		Pulse			Systolic			Diastolic			
													Increase		Reaction Time	Increase		Reaction Time	Increase		Reaction Time	
							Max.	Aver.	Max.	Aver.	Max.	Aver.	Max.	Aver.		Max.	Aver.		Max.	Aver.		
Lowsley	16	......	Bicycle	?	....	.....	35-95	51	65 17½′	32	40 30′	22	16-36	..	45′-100′	10	..	48′-60′	11	..	8′-35′	Reaction time 20′+; blood pressure to subnormal, but pulse remained above normal a long time
	6	......	Mod. exercise, swimming, tennis	½-2 hrs.	....	.....	..	..	..	..	..	..	..	..	31′ aver.	..	..	31′ aver.	..	..	21′ aver.	
Benedict	16	......	Fast running	100 yds.	....	.....	..	..	..	..	..	..	50	45	70′	36	45	70′	..	17	65′	+2
	16	......	Vigorous exercise, wrestling, running	.... 2-4 mi.	....	.....	..	..	..	..	..	..	70	39	60′	75	35	124′	40	25	80′	
	8	......	Fatiguing, running	5-9 mi.	....	.....	..	..	..	..	..	..	44	..	70′	..	..	70′	..	..	35′	
			Exhausting	10-20 mi.	....	.....	..	..	..	..	..	..	54	..	213′	39	..	232	39	..	160′	
			Bicycle	1.05 cal. 1.5 cal. 2.0 col. 2.25 cal.	60-64	.....	..	..	..	..	..	..	65 100 103 106	.. ..	150′+ 150′+ 150′+ 150′+							
MacMahon	11	Normal	Dumb-bells 5 lbs., arms	6,000 to 12,000 ft. lbs.	....	.....	..	..	..	..	..	..	..	41	180″	..	12	180″	..	..	.....	Effort syndrome; blood pressure, 15 second readings for 3 minutes
	50	Effort syndrome	Dumb-bells 5 lbs., arms	....	....	.....	..	..	..	..	..	..	..	30+	180″+	..	3-7	180″	..	..	.....	Divides all cases into five groups, from 2,000 to 10,000 foot-pounds
McCurdy	23	Normal	Lifting strength	....	....	.....	..	7	70	..	..	..	..	7	60″	..	..	120″				

Bowen	3 30 experiment	Normal, untrained	Bicycle, moderate	400 kg. per minute	....	.....	Sudden rapid rise, maximum 5′–10′ plateau; drop right after work stops						.... No exact figures									Blood pressure falls very rapidly after work to subnormal or normal, but pulse reaches a plateau and stays above normal for a long time
Cotton-Lewis	..	Controls	Lifted 20 lb. dumb-bells	200 ft. lbs. 400 ft. lbs. 800 ft. lbs. 1,200 ft. lbs.	....	....	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..	32 39 56 65	.. ..	60″ 110″ 160″ 200″	.. ..	9 18 25 36	50″ 110″ 185″ 260″				
Masing	......	Normal	Lifting weight with the leg	4 kg. per min. 4 min.	113 (19-21 yrs.) 111 (68-73 yrs.)	.....	19-39	29														
	9 19-23 yrs.	......	Lifting weight with one or both legs, Delio	2-5½ kg. in two periods	....	.....	27-39	33.6	29-49	38.4												
	3 38-50 yrs.	......	....	....	....	.....	31-43	37	34-59	49												
	4 58-81 yrs.	......	....	....	....	.....	17.5-40.5	26.3	24-66.5	51.5												
Moritz	6 2 exper. each, 21-32 yrs.	Normal	Delio (see Masing) leg or finger	567 kg. 25.2 420 6.4 264 16 216 14.4 162 21.6	84 84 64 68 68 64 72 68 56 56	140 145 133 127 142 138 155 158 128 120	16 16 49 22 22 8 18 22 24 ..	.. ..	45 30 7 23 30 15 16 25 16 25	.. ..	.. ..	.. ..	22 —4 8 ... 4* 4 4 10 8 ..	.. ..	35′ 7′ 12′+ 7′+ 11′ 7′+ 14′+ 11′ 12′ 13′	22 .. 7 8 10* 5 3 4 0 5	.. ..	35′ 17′ 9′+ 7′ 11′ 8′ 14′ 11′ 1′ 14′?	..	..	...	The quantity of fatigue, not the quantity of work determines the heights of the blood pressure. The blood pressure rises in proportion to the energy and will power to continue the exercise in spite of tiredness. Blood pressure and pulse taken at one minute intervals during and after exercise
		Myodegeneration	One leg Running	88 kg., 5 min. 66.8 kg., 19 min. 2 mi. 1 mi.	....	....	.. .. ..	.. .. ..	.. .. ..	.. .. ..	.. .. ..	.. .. ..	76 96 74	.. .. ..	107 15 60							

* Two minutes after exercise.

(100 yard dashes) causes a rise of about 45 mm. of the systolic blood pressure and of 45 beats per minute in the pulse rate. The reaction time of the pulse (return to normal) occurs within sixty minutes; wrestling delays still more the reaction time of both pulse and blood pressure. After exhaustive exercise (runs of ten to twenty miles) the circulatory reactions remain abnormal for several hours.

Cotton and Lewis [7] studied the effect of exercise with twenty pound dumbbells in soldiers. They reported that the blood pressure showed an abrupt rise at the beginning of exercise, a decided drop at its cessation and a return to normal within four minutes. The pulse rate was found to increase on the slightest effort, the maximum rise appearing at the end of work, to decline abruptly at cessation of work.

Cotton and Lewis stated that, in general, the amount of work determined the rise of systolic blood pressure, and the rate of work the rise of the pulse rate.

In summing up the work of these authors, the differences in their conclusions have to be ascribed to the differences in their technic and the lack of normal standards.

They all agree that (1) all forms of exercise increase the pulse rate and blood pressure; (2) the rise and the reaction time are proportionate to the quantity and the speed of exercise and (3) strength tests cause a sharper and higher increase of the pulse rate and blood pressure during exercise, the latter returning more quickly to normal in strength tests than in any other form of exercise.

The Effect of Posture on the Pulse Rate and Blood Pressure.—The literature on blood pressure and pulse in normal children is insufficient and inconstant. Therefore, we considered a careful study of this subject necessary. About 600 determinations were carried out on 100 children, between the ages of 6 and 15 years. The systolic and diastolic pressures, as well as the pulse rate, were taken in the standing, sitting and reclining postures. The determinations were made with the Baumanometer sphygmanometer by the auscultatory method. The cuff used was 9 cm. wide, and the right arm was always employed. Careful explanation as to the technic was given to every child so as to exclude the possibility of excitement. It proved advisable to begin with the standing posture. The first blood pressure reading was always discarded. At least three readings were taken at each sitting. In some instances, the reading was continued for as long as fifteen minutes, until constant figures were established. The same procedure was observed in the sitting position and finally in the lying. For ascertaining the diastolic pressure it is essential, especially in children under 10 years of age, to keep the arm at right angle to the body, so as to avoid constriction, otherwise pulse pressures of ten mm. and below may be obtained. The pulse rate was counted simultaneously by auscultation.

---

[7] Cotton, T. F., Rapport, D. L., and Lewis, T.: After Effects of Exercise on Pulse Rate and Systolic Blood Pressure in Cases of "Irritable Heart," Heart **6**:269, 1917.

TABLE 2.—Effect of Posture on Blood Pressure and Pulse—Age 6 Years

				Blood Pressure									Pulse		
				Lying			Sitting			Standing					
Subject	Age in Yrs.	Weight in Lbs.	Height in In.	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulsc Pressure	Lying	Sitting	Standing
B. D.	6	53.5	47.75	96	67	29	85	54	31	86	56	30	81	85	83
E. B.	6	47.5	44.5	97	66	31	84	55	29	90	62	28	79	91	90
M. E.	6	44.5	46	99	71	28	86	61	25	85	60	25	91	93	90
A. T.	6	56	48	102	76	26	94	70	24	97	75	22	110	121	125
4 cases	6	50.4	46.5	99	70	29	88	60	28	90	62	28	90	98	100

TABLE 3.—Effect of Posture on Blood Pressure and Pulse—Age 7 Years

				Blood Pressure									Pulse		
				Lying			Sitting			Standing					
Subject	Age in Yrs.	Weight in Lbs.	Height in In.	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Lying	Sitting	Standing
M. B.	7	53.5	49.75	105	73	32	88	62	26	90	64	26	73	79	78
E. B.	7	51	46.75	97	77	20	91	66	25	89	65	24	96	103	103
C. K.	7	58	47.5	104	77	27	99	74	25	97	72	25	84	97	95
L. D.	7	54.75	48	105	76	29	95	65	30	96	66	30	92	96	104
C. J.	7	50.75	48.75	92	62	30	77	58	29	77	50	27	87	96	102
J. M.	7	49.5	46.5	116	86	30	110	80	30	105	77	28	82	88	78
H. R.	7	47.25	46.75	93	63	30	82	55	27	79	51	28	88	93	95
T. S.	7	58	47.5	100	70	30	92	62	30	96	67	29	86	87	93
H. S.	7	45	46.75	102	85	17	88	70	18	87	70	17	98	105	102
U. W.	7	61.5	51	111	85	26	104	79	25	102	76	26	83	98	101
10 cases	7	52.8	47.9	102	75	27	94	67	27	92	66	26	87	94	95

TABLE 4.—Effect of Posture on Blood Pressure and Pulse—Age 8 Years

				Blood Pressure									Pulse		
				Lying			Sitting			Standing					
Subject	Age in Yrs.	Weight in Lbs.	Height in In.	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Lying	Sitting	Standing
H. B.	8	79.5	52.75	106	75	31	95	66	29	96	68	28	83	100	98
J. C.	8	57.5	48	107	78	29	95	65	30	95	66	29	86	101	101
O. F.	8	55	49	103	80	23	93	71	22	95	73	22	82	91	94
J. J.	8	51.5	51.5	99	76	23	91	67	24	91	68	23	69	75	73
M. G.	8	71.75	53.5	106	77	29	94	65	29	98	68	30	82	92	96
W. P.	8	59	49	103	79	24	94	71	23	91	69	22	81	89	88
G. S.	8	60.25	48	107	80	27	93	67	26	92	69	23	81	86	93
M. S.	8	60.25	49.75	95	71	24	86	63	23	85	62	23	78	96	103
J. P.	8	76.75	52.5	109	83	26	99	76	23	100	76	24	70	72	70
J. V.	8	55.75	48.5	103	78	25	90	64	26	93	64	27	79	84	78
10 cases	8	62.75	50.25	104	79	25	93	68	25	94	68	26	79	88	89

The figures in Tables 2 to 12 represent the averages of three or more determinations carried out on different days, though under conditions as alike as possible. The pulse rates found confirm the work of previous authors, the pulse rate being higher in the sitting than in the lying position and higher in the standing than in the sitting position. There is no constant increase with age in any of the three postures. There exists, however, a definite relation between the rate in the standing and the sitting posture, on the one hand, and the lying posture on the other. The average ratio $\frac{\text{Rate standing}}{\text{Rate sitting}} = 1.06$ (with a maximum of 1.16 and a minimum of 1.01). $\frac{\text{The rate standing}}{\text{Rate lying}} = 1.15$ (with a maximum of 1.328 and a minimum of 1.09). In the lying posture the average pulse rate for all ages equals 79, the probable error ± 3.069, the coefficient of variability 5.75; in the sitting posture the average pulse rate is 86, the probable error ± 3.97 and the coefficient of variability is 6.83; in the standing position 91 was found to be the average for the pulse rate, ± 3.02 for the probable error and 4.908 for the coefficient of variability.

TABLE 5.—EFFECT OF POSTURE ON BLOOD PRESSURE AND PULSE—AGE 9 YEARS

				Blood Pressure											
				Lying			Sitting			Standing			Pulse		
Subject	Age in Yrs.	Weight in Lbs.	Height in In.	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Lying	Sitting	Standing
J. B.	9	79	56	117	89	28	106	79	27	106	76	30	78	104	107
M. B.	9	65.5	53	111	87	24	100	75	25	198	74	24	75	90	93
I. G.	9	58.5	51.5	100	78	22	83	63	20	91	70	21	73	78	84
H. G.	9	61.5	51.5	106	84	22	93	69	24	95	73	22	96	103	104
H. G.	9	59	50.25	101	77	24	96	74	22	92	68	24	76	78	77
C. H.	9	67	53.25	98	77	21	89	68	21	87	66	21	82	90	93
M. L.	9	57	51	92	65	27	86	63	23	85	64	21	84	91	93
R. O.	9	68.75	53.5	104	76	28	99	73	26	98	70	28	92	103	108
H. W.	9	79.50	55.75	110	80	26	98	75	23	95	75	20	81	81	87
H. W.	9	62.5	49.5	99	67	22	94	74	20	90	70	20	67	77	79
10 cases	9	65.8	52.25	104	78	26	94	71	23	94	71	23	70	80	93

TABLE 6.—EFFECT OF POSTURE ON BLOOD PRESSURE AND PULSE—AGE 10 YEARS

				Blood Pressure											
				Lying			Sitting			Standing			Pulse		
Subject	Age in Yrs.	Weight in Lbs.	Height in In.	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Lying	Sitting	Standing
G. C.	10	67	52.75	100	82	18	89	67	22	94	75	19	87	100	114
H. A.	10	67	53.25	121	87	34	112	81	31	112	80	32	82	88	92
F. C.	10	71	55	105	73	32	95	66	29	97	70	27	70	74	90
A. H.	10	60	50.25	111	86	25	100	75	25	92	67	25	67	79	87
J. H.	10	104.5	56.25	114	85	29	102	75	27	101	72	29	73	79	82
C. J.	10	91	53.75	106	81	25	90	67	23	89	63	26	75	87	93
H. S.	10	74	55.5	102	78	24	90	69	21	92	70	22	82	93	92
B. G.	10	65.5	52.5	95	73	22	82	60	22	87	66	21	86	89	93
A. F.	10	64.5	52.25	106	83	23	88	64	24	92	69	23	76	82	76
9 cases	10	74	53.5	107	81	26	94	69	25	95	70	25	78	86	91

TABLE 7.—EFFECT OF POSTURE ON BLOOD PRESSURE AND PULSE—AGE 11 YEARS

				Blood Pressure											
				Lying			Sitting			Standing			Pulse		
Subject	Age in Yrs.	Weight in Lbs.	Height in In.	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Lying	Sitting	Standing
S. B.	11	74.5	55	103	78	25	95	67	28	99	72	27	99	79	89
G. D.	11	70	52.75	114	87	27	100	75	25	95	70	25	64	70	76
A. G.	11	79.5	55	115	86	29	102	73	29	104	76	28	85	88	98
P. H.	11	89.5	57.5	111	82	29	100	73	27	97	70	27	74	81	75
P. M.	11	82	54.75	111	80	31	100	73	27	103	76	27	59	71	89
E. R.	11	93.5	60.5	105	78	27	99	63	26	87	62	25	76	79	82
H. R.	11	73.75	52.75	100	75	25	87	64	23	88	64	24	79	87	82
L. S.	11	53	49	107	82	25	94	71	23	94	70	24	72	78	76
E. W.	11	60	52.5	104	78	26	94	69	25	94	69	25	76	81	92
V. B.	11	74	55.25	100	71	29	92	62	30	91	61	30	74	90	92
10 cases	11	75	54.5	107	80	27	96	69	26	95	69	26	76	80	85

TABLE 8.—EFFECT OF POSTURE ON BLOOD PRESSURE AND PULSE—AGE 12 YEARS

				Blood Pressure											
				Lying			Sitting			Standing			Pulse		
Subject	Age in Yrs.	Weight in Lbs.	Height in In.	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Lying	Sitting	Standing
J. B.	12	88.5	58	105	83	22	91	67	24	86	63	23	66	70	73
R. B.	12	78	55.75	107	81	26	96	70	26	95	71	24	72	92	93
B. B.	12	62.5	52.75	120	95	25	103	76	27	103	76	27	86	88	88
J. D.	12	68	52.5	118	92	26	104	80	24	102	75	25	76	89	91
T. B.	12	83	55	110	86	24	98	72	26	102	77	25	70	80	83
D. Z.	12	100	58.25	112	82	30	109	77	32	108	78	30	77	87	88
A. J.	12	74	57.25	116	91	25	107	86	21	101	78	23	64	66	68
A. G.	12	86.5	60	116	82	34	103	72	31	103	72	31	66	74	75
C. P.	12	91.5	57.5	110	85	25	102	74	28	94	67	27	90	98	98
M. R.	12	74	56	103	73	30	89	60	29	92	63	29	70	94	100
M. S.	12	81.5	54	104	77	27	96	72	24	99	71	28	73	78	79
J. T.	12	76	55.5	102	76	26	99	74	25	100	72	28	82	88	96
12 cases	12	80.3	56	110	84	27	100	73	26	99	72	27	74	84	86

TABLE 9.—EFFECT OF POSTURE ON BLOOD PRESSURE AND PULSE—AGE 13 YEARS

				Blood Pressure											
				Lying			Sitting			Standing			Pulse		
Subject	Age in Yrs.	Weight in Lbs.	Height in In.	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Lying	Sitting	Standing
P. C.	13	92	60	103	73	30	96	67	29	102	72	30	82	98	101
M. B.	13	95	60	113	84	29	102	74	28	95	66	29	73	89	93
B. C.	13	88	60	101	78	23	95	74	21	96	76	20	73	85	81
D. H.	13	90	59	113	84	29	109	81	28	102	78	24	86	94	103
C. J.	13	95	59	105	74	31	87	65	22	88	68	20	68	86	94
W. M.	13	122	63	118	83	35	109	75	34	108	75	33	80	94	93
E. L.	13	75	56	103	65	38	93	53	40	97	55	42	74	78	80
B. M.	13	80	56	107	67	30	95	66	29	96	66	30	81	86	91
C. P.	13	78.5	55	106	81	25	101	72	29	101	74	25	83	84	96
A. P.	13	112.5	62	124	93	31	106	75	31	104	73	31	88	92	91
C. S.	13	90	60.5	100	72	28	99	70	29	100	73	27	69	73	76
L. S.	13	83	60.75	92	58	34	81	57	24	81	53	28	74	80	90
M. S.	13	85	59.75	97	70	27	89	65	24	93	68	25	75	83	85
L. W.	13	124	66	117	79	32	99	72	27	110	79	31	77	82	87
M. W.	13	100	67	119	85	37	113	80	32	112	80	32	78	76	76
D. Z.	13	99	61	111	88	23	99	75	23	99	76	24	86	88	92
16 cases	13	94	59	108	76	30	98	68	28	99	68	28	78	85	89

TABLE 10.—EFFECT OF POSTURE ON BLOOD PRESSURE AND PULSE—AGE 14 YEARS

				Blood Pressure											
				Lying			Sitting			Standing			Pulse		
Subject	Age in Yrs.	Weight in Lbs.	Height in In.	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Lying	Sitting	Standing
H. B.	14	118	63.2	114	83	31	100	70	30	92	63	29	90	98	101
J. B.	14	109	63	116	86	30	110	76	34	112	79	33	77	85	93
J. C.	14	93	60	105	76	29	108	84	24	100	76	24	60	74	82
A. F.	14	85	59	106	80	26	95	69	26	94	70	24	69	89	95
H. F.	14	85	59	111	83	28	97	70	27	104	78	26	70	80	78
R. G.	14	122	63	121	97	24	101	73	28	102	73	29	75	72	76
H. H.	14	75	56	105	84	19	96	74	22	99	78	21	79	91	94
C. H.	14	93	59	116	88	28	109	77	32	103	76	27	79	85	89
A. K.	14	74	51	115	87	28	106	81	25	107	86	21	72	82	82
M. K.	14	96	58	112	83	29	104	75	29	99	69	30	83	91	92
H. P.	14	93	63	109	81	28	93	64	29	92	65	27	97	102	105
E. R.	14	97	59	110	86	24	98	75	23	96	61	25	73	85	90
H. R.	14	99	62	124	95	29	112	86	26	113	87	26	72	78	84
M. S.	14	120	65	139	93	46	118	80	38	117	77	40	80	85	86
W. T.	14	76	58	109	85	24	100	74	26	97	70	27	73	81	80
F. L.	14	109	61	122	86	36	112	78	34	118	81	37	84	91	94
16 cases	14	96	59	114	85	28	104	76	28	102	74	28	78	79	88

Analyzing the blood pressure readings in Table 12 one notices, on the whole, a slight increase of the systolic pressure from year to year in all three postures. This is not true of the diastolic pressure. The pulse pressures, however, are fairly constant for all ages and all postures. The averages of the systolic, diastolic and pulse pressures in the three positions, their probable error and coefficient of variability are recorded in detail in Table 13.

TABLE 11.—Effect of Posture on Blood Pressure and Pulse—Age 15 Years

				Blood Pressure											
				Lying			Sitting			Standing			Pulse		
Subject	Age in Yrs.	Weight in Lbs.	Height in In.	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Lying	Sitting	Standing
E. B.	15	104	62.5	115	86	30	108	76	32	102	67	35	87	95	108
A. B.	15	125	68.5	116	83	33	86	55	31	104	58	46	..	84	
A. F.	15	116	63	116	75	41	100	67	33	96	64	32	72	82	91
L. P.	15	110	62.5	127	96	31	107	74	33	108	76	32	86	100	101
M. R.	15	102	60.5	108	79	29	102	70	32	101	72	29	78	80	88
W. S.	15	107	64	115	85	30	101	70	31	100	70	30	81	94	93
6 cases	15	110.7	63.5	116	84	32	101	69	32	102	68	34	81	89	96

TABLE 12.—Effect of Posture on Blood Pressure and Pulse—Ages 15-6 Years

				Blood Pressure											
				Lying			Sitting			Standing			Pulse		
of Cases	Age in Yrs.	Weight in Lbs.	Height in In.	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Lying	Sitting	Standing
6	15	110.7	63.5	116	84	32	101	69	32	102	68	34	81	89	96
16	14	96	59	114	85	28	104	76	28	102	74	28	78	79	88
16	13	94	59	108	76	30	98	68	28	99	68	28	78	85	89
12	12	80.3	56	110	84	27	100	73	26	99	72	27	74	84	86
10	11	75	54.5	107	80	27	96	69	26	95	69	26	76	80	85
9	10	74	53.5	107	81	26	94	69	25	95	70	25	78	86	91
10	9	65.8	52.25	104	78	26	94	71	23	94	71	23	70	80	93
10	8	62.75	50.25	104	79	25	93	68	25	94	68	26	79	88	89
10	7	52.8	47.9	102	75	27	94	67	27	92	66	26	87	94	95
4	6	50.4	46.5	99	70	29	88	60	29	90	62	28	90	98	100

TABLE 13.—Statistical Data for Blood Pressure in Various Postures

	Standing			Lying			Sitting		
	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Pulse Pressure
Average..................	96	68	27	108	80	28	96	69	27
Probable error...........	2.629	2.196	1.847	3.406	3.047	1.366	2.971	2.664	1.61
Coefficient variability...	4.061	4.787	10.14	4.676	5.645	7.231	4.581	5.724	8.84

The probable error for the systolic and diastolic pressures of all ages ranges from ± 1.5 to ± 3.4, the coefficient of variability of the systolic and diastolic blood pressures lies between 4.0 and 5.6 for the three postures. The error for the pulse pressure is about ± 2 and the coefficient of variability from 7 to 10.

Comparing the systolic and diastolic blood pressures in the three postures, one finds that the blood pressure in the lying position is invariably higher than that in the sitting position, and that in the sitting position it is practically always higher than that in the standing position. This differs with the conclusions of some investigators on the blood pressure in normal adults. It should be emphasized at this point that the technic remained the same throughout all readings and that the blood pressure in the supine position was taken after those in the other positions. In some instances, the order was changed with no change in the results. The average ratio of $\frac{\text{Blood pressure lying}}{\text{Blood pressure sitting}} = 1.14$ (maximum $= 1.15$, minimum $= 1.085$) and the average ratio of $\frac{\text{Blood pressure lying}}{\text{Blood pressure standing}} = 1.11$ (maximum equals 1.127, minimum equals 1.09). As stated before, the average ratio of the pulse rate in standing to sitting was 1.06 and that in standing to lying 1.15. The ratio for the systolic blood pressures in the various positions, is practically inversely proportional to the ratio of the pulse rates in the same position. In other words, the $\frac{\text{Blood pressure lying}}{\text{Blood pressure standing}}$ about $= \frac{\text{Pulse standing}}{\text{Pulse lying}}$

TECHNIC AND PLAN OF WORK

Ergometer.—It has been mentioned above that the lack of uniformity in technic on the part of previous authors made impossible deductions for standards on the circulatory reactions after exercise. To accomplish this the authors decided to use the ergometer, in a modified form (Figs. 1 and 2). A bicycle is made stationary by fastening it to a wooden platform. The electric brake (used by other experimentors) is supplanted by a mechanical brake (Prony Brake)[8] (*b*) which consists of wooden strips attached to a piece of leather belting. The resistance to work is standardized by means of a screw (*c*) and measured on a scale (*d*) of four pound capacity, with sixteen divisions for each pound. The pointer (*e*) on the scale is practically prevented from vibrating by a damper (*f*) on the beam (*g*), the length of which is $\frac{63.025 \text{ inches}}{4\text{x}12}$ (one-fourth of the standard size). The wheel (*h*) of the pulley carries a cyclometer (*i*) which records the number of revolutions for a given period. Daily lubrication of the brake allows for smooth riding. Two bicycles were built, one for children 58 inches in height and over, the other for smaller children. The experiments were carried out in one of the Minneapolis Public Schools. All the subjects were within the normal limits of height, weight and general physical development. Complete physical examination was made in

---

[8] A foot-pound equals the work done in lifting a pound one foot high against the force of gravity. There is about 1% error on account of friction of the bicycle chain and in the reading of the scale. The formula used depends upon the lifting of a load around a circle of which the beam is the radius. We want to express our sincere thanks to T. B. Rowley and B. J. Robertson, Prof. and Associate Prof. of Mechanical Engineering, respectively, for their help in the building of the Ergometer.

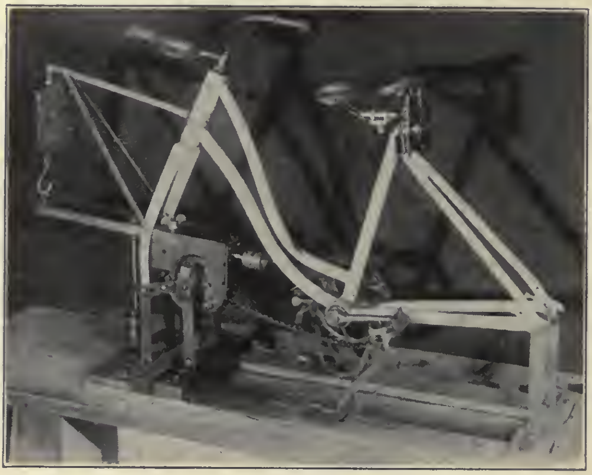


Fig. 1.—The ergometer is fastened to a bicycle frame.

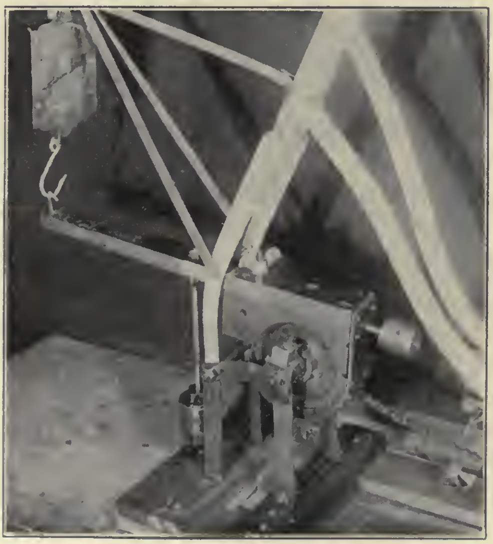
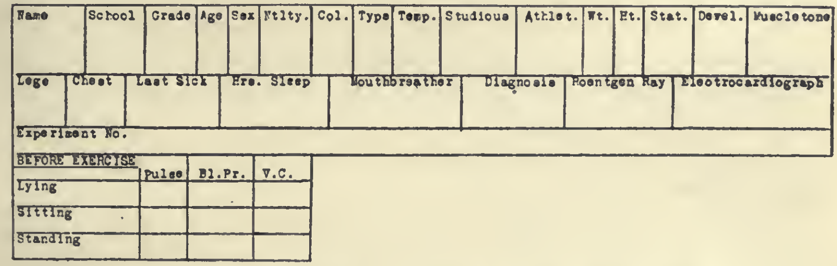


Fig. 2.—This illustration shows in detail how the ergometer is attached to the front of the bicycle frame.

every instance so as to exclude those afflicted with rhinitis, tonsilitis, bronchitis and other infections occurring frequently during the winter. With very few exceptions the children were zealous in their efforts to prove that "they were strong" and that "their hearts were good." The competitive spirit so splendidly developed in the American child resulted in delightful cooperation.

First a questionnaire (Fig. 3) was answered. Next the pulse and blood pressures (systolic as well as diastolic) were determined in the three postures. Before the experiment on the ergometer, the child was made familiar with the technic by explanation and by a demonstration on another child.

On the next day, the blood pressure was again taken standing and sitting on the bicycle as on the previous day. The blood pressure readings in the sitting posture were repeated until uniform. The pulse rate was ascertained simultaneously with the stethoscope.



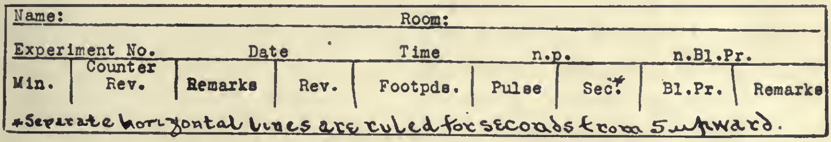
Name	School	Grade	Age	Sex	Ntlty.	Col.	Type	Temp.	Studious	Athlet.	Wt.	Ht.	Stat.	Devel.	Muscletone

Legs	Chest	Last Sick	Hrs. Sleep	Mouthbreather	Diagnosis	Roentgen Ray	Electrocardiograph

Experiment No.

BEFORE EXERCISE	Pulse	Bl.Pr.	V.C.
Lying			
Sitting			
Standing			

Fig. 3.—Data sought by means of the questionnaire.



Name: Room:

Experiment No. Date Time n.p. n.Bl.Pr.

Min.	Counter Rev.	Remarks	Rev.	Footpds.	Pulse	Sec.*	Bl.Pr.	Remarks

*Separate horizontal lines are ruled for seconds from 5 upward.

Fig. 4.—Headings on blank used to record the observations made on each child.

By this time the child had become accustomed to the apparatus, the blood pressure cuff and the workers. The feet of the subject were fastened to the pedal by means of two straps in crosswise adjustment. The blood pressure and pulse rate were again determined. This procedure was absolutely necessary for obtaining correct readings, the irregularities and inconstancies being thus eliminated. If, in spite of all these precautions, the first reading of the blood pressure in the sitting position was 4 mm. above the following readings, it was discarded. Then the riding capacity of the child was tested. The child was instructed to go as fast and as long as possible and not to stop until so advised. The number of revolutions and the duration of the experiment were noted on a blank as shown in Figure 4. It took from five to seven seconds to adjust the screw on the brake. All the signs and symptoms observed during exercise were also recorded on the chart. Severe perspiration, as well as extreme dyspnea, were taken as the index of maximum physical effort. Thirty seconds before the end of the experiment the child was reminded to lay its arm on the wooden support at the word "stop." The blood pressure cuff was kept partly inflated for the last three seconds so as to avoid any delay in determining the first blood pressure reading after exercise. Thus, in the majority of experiments the first reading was taken within from three to five minutes after exercise, and only in rare instances as late as after ten seconds. The readings of the blood pressure were repeated at periods of ten seconds for the first minute and at periods of thirty seconds thereafter until the blood pressure had returned within 2 mm. of the preexercise level. In the pulse five beats per minute were allowed as a limit of normal variation. It was found in a hundred determinations that the average difference between the highest and lowest blood pressure readings was 2 mm., and the average variation in pulse rate was five beats.

The technic of the dumbbell and staircase exercise will be described in detail later.

Comparison of the Effect of Different Types of Exercise on the Circulatory Reactions.—It has been determined by other investigators that short periods of work, especially work involving speed rather than strength, always causes an increase in the pulse rate, the latter returning to normal within a few minutes, depending on the speed and the kind of work. The dumbbells are the most popular apparatus with which the clinical physiology of muscular exercise has been studied in the last few years. Wilson,[9] experimenting with dumbbells at the rate of two seconds for each swing, found that in 63 per cent. of her subjects who had reached the point of fatigue (+ + + dyspnea), the rise in pulse rate was proportional to the increase in work. In 60 per cent. the maximum rate accompanied the maximum amount of work. In 52 per cent. of the experiments the reaction time to normal was 120 seconds, and in 28 per cent. the pulse became subnormal at the end of two minutes. In 13 per cent. the pulse remained above normal at the end of two minutes. In the majority of her cases the pulse returned to normal within one hundred and twenty seconds whether the subjects were only slightly fatigued or markedly exhausted. She did not state whether the pulse rate in the mild exercises in which no dyspnea was produced returned to normal earlier than in the more severe exercises.

---

[9] Wilson, May G.: The Circulatory Reactions to Graduated Exercise in Normal Children, Am. J. Dis. Child. **20**:188, 1920. Exercise Tolerance of Children with Heart Disease as Determined by Standardized Test Exercises, J. A. M. A. **76**:1629 (June 11) 1921.

Wilson also claims that the type of curve showing a delayed rise of the blood pressure and a prolonged fall "was present in 88 per cent. of the experiments and in 85 per cent. it was accompanied by clinical symptoms of marked dyspnea and fatigue. The rise of blood pressure varied from 2 to 55 mm. The maximum blood pressure reading was 160. The rise varied directly with the increased quantity of exercise, and in 92 per cent. of the experiments the rise was proportional to the amount of dyspnea and fatigue."

In view of Wilson's claim it was thought expedient to include a similar study in this treatise.

Dumbbell Arm Exercise.—Thirteen experiments were carried out, the subjects lifting two four-pound dumbbells from the shoulders to full arm length. The child swung to the limit of his capacity. The blood pressure and pulse were taken before and immediately after exercise. The circulatory reactions are recorded in Table 14. It can be seen that the average rise of the blood pressure amounted to 15.2 mm. in the smaller children, who averaged forty swings, and 32.6 mm. in the older children, who averaged ninety swings. The average reaction time was 221 seconds for all subjects. The maximum rise occurred between 5 and 30 seconds in approximately 70 per cent. of the cases. In none of the experiments was a delayed rise present, although the subjects showed subjective signs of exhaustion. The pulse rate returned to normal within two minutes in practically all the cases (Table 15 A). The increase in the pulse rate averaged 42.6 beats.

Full Length Lift.—In thirty-one experiments two 4-pound dumbbells were lifted from the floor the length of the arm above the head, one full swing lasting two seconds. Wilson's technic was followed. It was found that the pulse rate and the blood pressure increased in proportion to the number of swings. The average rise in the pulse rate was 34.9 after ten swings, 58 after thirty swings and 72.6 beats after sixty swings (Table 15 B.). The blood pressure rose on an average of 23.6 mm. after ten swings, 28.9 mm. after thirty swings and 32.7 mm. after sixty swings. The reaction time of the blood pressure also increased with an increase in the number of swings, the reaction time being 154 seconds after ten swings, 213 seconds after thirty swings and 281 seconds after sixty swings. The maximum reading of the blood pressure obtained between 5 and 30 seconds in 100 per cent. of the experiments after ten swings, in 37 per cent. after thirty swings and in 70 per cent. after sixty swings. Wilson claims that there is an increase in the time of maximum reading with

TABLE 14.—Effect of Different Types of Exercise on the Circulatory Reactions

Type of Exercise and Subject	Age in Years	Weight in Pounds	Height in Inches	Number of Swings	Foot-Pounds of Work	Pulse						Systolic Blood Pressure						
							After Exercise						After Exercise					
						Before Exercise	Maximum Reading	Time of Maximum Reading, Sec.	Rise	Reaction Time, Sec.		Before Exercise	First Reading, Mm.	Time of First Reading, Sec.	Maximum Reading, Sec.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.
Dumbbells, Body Exercise																		
H. G.	9	61½	52¼	10	412	90	120	5	30	90		101	113	5	120	20	19	180
				30	1,236	100	170	5	70	120		98	115	10	123	35	25	180
				50	2,060	90	160	10	70	270+		98	117	10	129	30	31	300
I. P.	9	76¾	52½	10	422	86	110	10	24	60		103	127	10	132	20	29	180
				30	1,266	90	160	5	60	60		107	122	10	132	40	25	150
				60	2,532	90	170	10	80	60		107	130	10	147	50	40	300
H. S.	10	74	55¼	10	435	90	130	10	40	40		96	109	10	112	30	16	150
				30	1,305	90	150	5	60	60		91	109	20	115	30	24	150
				60	2,610	90	170	5	80	150+		90	118	10	122	20	32	180+
A. H.	11	60¼	50¼	10	402	76	120	5	44	150		96	117	10	120	20	24	120
				30	1,206	78	132	5	54	90		99	124	10	125	10	26	180
				60	2,402	76	144	5	68	180+		98	133	10	135	10	37	270+
S. B.	11	75	55½	10	437	84	120	10	36	40		95	112	10	116	20	21	90
				30	1,310	74	120	5	46	60		94	116	10	116	10	20	270
				53	2,316	78	120	5	42	50		98	115	10	121	40	23	150
A. G.	11	79¼	54¾	10	430	90	100	10	10	50		108	130	10	132	10	24	180
				30	1,290	90	140	10	50	60		110	120	10	130	50	20	390
				10	430	90	120	10	30	90		111	116	10	126	20	15	150
				30	1,290	100	140	5	40	50		111	128	10	136	20	25	300
				60	2,580	90	170	10	80	210		115	140	10	150	45	35	360
B. Br.	12	62½	52¾	10	418	72	115	5	43	50		99	127	5	133	20	34	150
				30	1,256	78	132	5	54	60		111	149	5	149	5	38	240
				60	2,512	78	144	5	66	150		101	138	5	145	30	44	390
J. D.	12	68	52½	10	416	84	120	10	36	20		111	135	5	148	20	39	150
				30	1,248	84	144	5	60	40		110	138	5	147	20	37	180
				60	2,496	84	144	5	60	40		113	145	5	148	20	35	210
R. B.	12	78	55¾	10	437	90	144	5	54	120		111	119	10	130	30	19	180
				30	1,310	96	168	5	72	90		105	129	5	147	40	42	270
				60	2,621	84	180	5	96	150		102	130	10	141	30	39	330
M. H.	15	75	56	10	440	90	120	5	30	90?		107	128	5	129	5	22	120
				10	440	90	132	5	42	40		96	111	10	117	20	21	150
				30	1,320	84	132	10	48	60		100	128	10	136	30	36	270
				60	2,640	84	168	5	84	60		99	138	5	150	30	51	390
Dumbbells, Arm Exercise																		
I. C.	8	57½	48	40	360	90	132	10	42	60		98	108	10	102	20	14	150
				40	360	90	132	10	42	60		102	118	10	118	20	16	210
M. S.	8	60½	49¾	40	360	90	120	10	30	40		103	102	20	103	20	13	180
				30	324	90	120	30	30	60		83	101	30	101	30	18	300

G. S.	8	60¼	48	40	360	90	120	10	30	50	92	104	20	108	40	16	180
				50	450	84	132	10	51	60	91	105	20	105	20	14	180
M. K.	14	96	48	64	787	96	120	10	24	60	104	129	10	129	10	25	150
				75	922	84	108	10	24	40	99	111	20	116	40	17	180
				81	996	84	96	10	12	45	104	122	10	127	20	23	150
				86	1,273	78	132	10	54	150	106	121	10	128	30	22	180
F. L.	14	109½	61	90	1,305	78	156	20	78	40	114	137	20	149	30	35	270
				100	1,450	84	144	10	60	40	106	152	10	159	40	53	
				110	1,595	84	132	10	48	40	117	157	5	159	5	42	240
				125	1,813	84	156	5	72	90	114	155	10	158	30	44	300
Staircase Test																	
I. C.	8	57½	48	Three flights of Stairs	1,311	100	216	20	116	180	101	122	30	125	40	24	420
					1,311	100	168	30	68	180	101	124	30	127	40	26	360
G. S.	8	60¼	48		1,581	96	180	10	84	360	98	128	30	128	30	30	360
					1,581	96	168	30	72	90	98	127	30	128	30	30	420
M. S.	8	60¼	49¾		1,581	96	156	20	96	90	96	105	20	123	40	27	330
					1,581	96	156	20	60	60	96	104	10	116	30	20	270
					1,581	98	168	30	70	120	91	112	30	112	30	21	330
					1,581	96	180	10	84	150	91	93	10	109	50	17	270
M. K.	14	96	58		2,520	83	168	30	85	240	106	146	30	149	50	43	
					2,520	84	156	30	72	450+	106	139	30	149	50	43	390
F. L.	14	109½	61		2,890	84	180	10	96	60	117	144	10	148	20	31	360
					2,890	96	168	10	72	120	119	150	20	162	40	43	
					2,890	84	144	10	60	150	117	144	10	158	25	40	
					2,890	84	156	10	72	150	117	154	10	158	30	41	480
					2,894	84	180	10	96	90	117	167	10	167?	10	50?	390
Ergometer Readings for 1, 2, 3 and 4 Min.				No. of Min.													
I. C.	14	93	60¾	1	5,838	84	156	5	72	480+	109	146	5	163	30	54	360
					5,368	90	168	5	78	210	112	141	5	155	20	43	270
					4,508	84	168	5	84	270	109	146	20	149	50	40	240
					5,281	84	168	5	84	180	108	147	5	149	5	41	270
				2	9,941	84	180	5	96	540	116	147	5	163	40	47	300
				3	12,465	84	180	5	96	600+	102	156	5	171	50	67	660+
H. B.	14	118	63	1	6,268	108	168	5	60	180	107	157	5	157	5	57	390
					6,199	100	168	5	68	360	105	151	5	163	50	58	360
					9,748	100	...	..	..	...	...	...	..	164	10	52	390
				2	10,788	102	168	5	66	360	106	157	5	161	40	55	390
					11,624	100	168	5	68	300	103	167	5	173	50	70	510
D. G.	13	100	58¼	1	4,041	108	144	20	36	50	120	124	5	126	5	6	50
					3,793	120	160	5	40	150	110	125	5	134	40	24	360
					4,370	105	150	5	45	180	110	125	5	134	10	24	300
				2	8,165	108	156	5	48	600+	120	154	10	154	10	34	270
					8,248	105	150	5	45	180	110	120	5	132	20	22	300
				3	11,875	108	144	36	36	360	112	133	5	143	20	31	300
					12,044	105	170	5	65	450+	110	125	5	142	5	27	240
					12,040	108	168	5	60	360+	115	140	5	142	5	23	390
				4	14,886	108	168	5	60	360+	115	140	5	142	5	27	240
J. D.	12	68	48½	1	2,844	90	148	5	54	120	125	148	5	157	10	32	180
					3,218	90	168	10	78	360+	125	149	5	160	10	35	270
					3,154	90	168	10	78	150	123	158	5	158	5	35	300
					3,402	96	156	5	60	50	110	142	5	149	20	39	300
				2	6.432	88	168	5	80	270	114	142	5	160	20	46	300
					4,885	96	180	5	84	120	119	140	5	164	20	45	330
					6.066	96	180	5	84	116	162	5	..	166	10	45	390
				3	8,940	96	168	5	72	420	114	158	5	160	5	72	420
					8,660	102	168	5	66	60	109	158	5	160	5	51	450
					8,472	96	174	5	78	210	109	151	5	158	20	49	300

TABLE 14.—EFFECT OF DIFFERENT TYPES OF EXERCISE ON THE CIRCULATORY REACTIONS—(*Continued*)

Type of Exercise and Subject	Age in Years	Weight in Pounds	Height in Inches	Number of Min.	Foot-Pounds of Work	Pulse					Systolic Blood Pressure						
						Before Exercise	After Exercise				Before Exercise	After Exercise					
							Maximum Reading	Time of Maximum Reading, Sec.	Rise	Reaction Time, Sec.		First Reading, Mm.	Time of First Reading, Sec.	Maximum Reading, Sec.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.
A. H.	10	60	50¼	1	2,907	96	148	10	52	120	114	162	5	164	5	50	270
					2,537	90	148	10	58	50	112	157	5	157	5	45	270
					2,660	96	168	5	72	50	109	134	5	145	30	36	360
				2	5,505	96	168	10	72	360	116	162	5	162	5	46	270
					5,690	90	144	5	54	420+	111	167	5	167	5	56	360
					5,568	96	168	5	72	360	116	148	5	152	10	53	420
				3	7,979	96	168	5	72	390+	114	143	5	155	30	41	390
					7,547	108	180	5	72	180	114	139	5	154	10	40	210
					8,525	96	180	5	84	510+	109	132	5	148	30	39	390
I. C.	8	57½	48	1	2,185	95	160	5	55	120	100	128	5	131	10	31	360
					2,145	95	160	5	65	240	100	121	5	126	5	26	300
				2	3,959	95	140	5	45	240	100	130	5	132	5	32	240
					3,918	95	150	5	55	180	100	127	5	132	20	32	390
				3	5,449	95	160	5	65	360	100	130	5	134	10	34	330
					6,032	90	150	5	60	360	97	125	5	127	5	30	360
B. M.	13	80	56	1	4,929	102	168	5	66	180	103	132	5	132	5	29	270
				2	7,620	100	168	5	68	180	96	130	5	138	20	42	270
D. H.	13	90	59¼	1	5,953	96	156	15	60	150	112	122	30	122	30	10	120
C. P.	13	....	....	1	4,451	108	...	..	..	...	...	...	..	145	30	35	360
G. P.	12	88½	58	1	4,931	84	156	10	72	270+	100	130	20	132	20	32	270
L. R. S.	12	80	56	1	2,148	105	144	5	39	40	89	120	10	120	10	31	270
W. T.	14	76	58	1	5,294	96	156	30	60	240+	109	130	30	130	30	21	240
R. B.	12	78	55¾	2	7,076	120	168	20	48	270	118	147	40	147	40	29	270
J. T.	12	76	55½	2	7,883	90	180	5	90	420+	94	100	5	109	50	15	300
M. R.	12	74	56	2	4,657	96	144	5	48	150+	110	142	30	142	10	32	
M. H.	12	74	56	2	10,890	90	180	10	90	420+	95	139	20	144	40	49	540+
A. G.	11	80	54¾	2	7,517	90	168	5	78	480	109	143	5	148	20	39	300
G. G.	6	47½	44	2	2,164	108	120	10	12	30	97	132	10	136	30	39	600
M. F.	14	85	59½	3	13,842	...	...	..	..	...	...	...	..	166	10	59	390
P. C.	13	92½	60¾	3	11,365	108	192	10	84	450	105	134	10	134	10	29	360
H. A.	10	67	53¼	3	8,155	108	168	5	60	300	125	166	5	147	20	49	270
D. Z.	13	99½	61	4	13,531	108	180	10	72	390	98	144	30	144	30	46	420
C. P.	12	91½	57½	4	12,776	105	160	20	55	600+	105	148	10	154	20	49	330
E. W.	11	60	52¼	4	13,010	102	180	10	78	240	113	147	5	149	5	36	300
A. F.	10	60	51	4	8,957	104	...	..	..	270	104	130	5	140	10	36	300
H. W.	9	61½	59	4	9,337	78	...	..	..	480+	101	153	5	162	20	61	300
S. B.	11	75½	55½	5	11,018	84	...	..	..	360+	102	122	5	129	30	22	330

an increase in swings. This is not borne out by Table 14; the majority of the cases showed the maximum readings within 30 seconds, only a small number at 40 and 50 seconds and none at 60 seconds or later.

Staircase Exercise.—In order to determine the effect of speed tests on the circulatory reactions, fifteen determinations were made, each child running up three flights of stairs. The average length of time for the run was fifteen seconds. The first blood pressure reading was taken within fifteen seconds after exercise. The amount of work performed by each child is recorded in Table 14. The pulse rate increased on an average of 47.1 beats per minute and the blood pressure 33.7 mm. The average reaction time of the pulse rate was 150 seconds, that of the blood pressure was 334 seconds. In 53.3 per cent. of the experiments (Table 15 C) the maximum reading occurred between 5 and 30 seconds. None of the experiments showed a delayed rise.

Ergometer.—PULSE RATE.—A number of children were allowed to ride the ergometer for periods of one, two, three and four minutes (Table 16). The children rode to the rythm of a metronome, so as to perform as equal amounts of work as possible. The average work for one minute was 4,279 foot pounds; for two minutes, 6,976 foot pounds; for three minutes, 9,690 foot pounds and for four minutes, 12,083 foot pounds. The rise in the pulse rate was 62.3 beats for one minute, 68.5 for two minutes, 65.8 for three minutes and 62.8 beats for four minutes. The reaction time of the pulse was 191 seconds, 319.5 seconds and 390 seconds, respectively, for the one, two, three and four minute exercises. Comparing the increase in the pulse rate after one minute with that after two minutes in the same subject, one finds an increase proportional to the work in four subjects, a decrease in one subject, while two subjects exhibit the same rise after the one minute as well as after the two minute exercise. Two subjects had a rise in pulse rate higher after three minutes exercise than after two minutes; in two subjects the pulse rate reached the same level, while one subject had a lower rise after three than after two minutes.

BLOOD PRESSURE (Table 17).—The blood pressure was determined simultaneously with the pulse rate. The rise of pressure was 36.5 mm. after the one minute, 39.8 mm. after two minutes, 31.2 mm. after three minutes and 42.6 mm. after four minutes. The time of maximum reading was 23.2 seconds, 28.1 seconds, 25 seconds and 36.2 seconds, respectively. The reaction time was 287 seconds, 339 (+) seconds and 330 seconds for the one, two and three minute exercise. In general, the blood pressure rises are higher after two minutes' exercise than after one minute; in the majority of the cases the blood pressure rise is greater after the three minute exercise than after the two minute exercise.

TABLE 15.—A. Reaction Time of Pulse After Different Types of Work

Sec.	Dumbbell				Staircase	Ergometer			
	Body 10	Body 30	Body 60	Armlift, Exhaustive		1 Min.	2 Min.	3 Min.	Exhaustive
40	3	1	1	5	..	1	..	..	..
50	2	1	1	2	..	4	..	..	..
60	1	6	1	5	1	1	..	1	..
90	1	1	..	1	3	..	..	..	..
120	1	1	..	..	2	3	1	..	..
150	1	..	2	1	3	2	..	..	..
180	..	..	..	..	2	4	3	1	..
210	..	..	1	..	..	1	..	1	..
240	..	..	..	..	1	1	1	..	..
270	..	..	..	..	..	2	3	..	..
300	..	..	..	..	1?	..	..	1	..
360	..	..	..	..	..	1	2	3	..
390	..	..	..	..	..	..	..	1	..
420	..	..	..	..	..	..	1	1	..
450	..	..	..	..	1?	..	..	1	..
480	..	..	..	..	..	..	1	..	..
540	..	..	..	..	..	..	1	..	..
600+	..	..	..	..	..	..	1	2	All

B. Reaction Time of Blood Pressure After Different Types of Exercise

Sec.	Dumbbell				Staircase	Ergometer			
	Bodylift			Armlift, Exhaustive		Exhaustive	1 Min.	2 Min.	3 Min.
	10	30	60						
40	..	..	..	..	..	..	..	..	..
50	..	..	..	..	..	..	1	..	..
60	..	..	..	..	..	..	..	..	..
90	1	..	..	..	..	..	1	..	..
120	2	..	..	..	..	..	..	..	..
150	5	3	1	3	..	3	..	..	..
180	2	4	..	5	..	6	1	..	..
210	1	..	1	1	..	18	..	..	1
240	..	1	..	1	..	17	1	2	1
270	..	2	1	..	1	17	9	4	1
300	..	1	1	1	2	23	4	5	2
330	..	..	1	..	2	21	..	1	1
360	..	..	1	..	3	15	6	2	2
390	..	1	2	1	2	18	2	3	2
420	..	..	..	..	2	12	..	1	1
450	..	..	..	..	..	3	..	..	1
480	..	..	..	..	1	..	..	..	..
510	..	..	..	..	..	1	..	1	..
540	..	..	..	..	..	1	..	..	..
570	..	..	..	..	..	1	..	..	..
600	..	..	..	..	..	1	..	..	..
Delayed time	..	..	..	1	2	18	..	..	1
No. of cases	11	12	8	13	13	158	25	21	12
Aver.	154	213	281	221	334	312	286	377	327

C. Time of Maximum Reading of Blood Pressure After Different Types of Work

Sec.	Ergometer			Dumbbell				Staircase
	1 Min.	2 Min.	3 Min.	Body 10*	Body 30*	Body 60*	Armlift	
5	8	3	5	2	1	..	1	..
10	6	4	4	1	2	1	1	1
20	3	6	3	8	2	2	5	2
30	5	1	2	2	3	4	4	5
40	1	4	..	..	2	2	3	4
50	2	2	2	..	1	1	..	3
60	..	..	..	..	..	..	..	..
No. cases	25	18	16	12	11	10	14	15

* Number of swings.

TABLE 16.—REACTION OF PULSE TO MEASURED AMOUNTS OF WORK

Subject	Age in Years	Load in Lbs.	1 Minute			2 Minutes			3 Minutes			4 Minutes			Remarks
			Foot-pounds of Work	Rise	Reaction Time, Sec.	Foot-pounds of Work	Rise	Reaction Time, Sec.	Foot-pounds of Work	Rise	Reaction Time, Sec.	Foot-pounds of Work	Rise	Reaction Time, Sec.	
J. C.	14	2	^{1} 5,838	72	480+	^{5} 9,941	96	540	^{6} 12,465	96	660+	......	..	...	Exp. 2 taken 1 hour after Exp. 1; Exp. 3 taken 45 min. after Exp. 2; Exp. 4 taken 2 hours after Exp. 3; Exp. 5 taken 30 min. after Exp. 4
		2	^{2} 5,368	68	210										
		2	^{3} 4,508	84	270										
		2	^{4} 5,281	84	180										
H. B.	14	2	^{1} 6,268	60	180	^{3} 10,788	66	360	......	..	...	......	..	...	Exp. 2 taken 35 min. after Exp. 1; Exp. 3 taken 2 hours after Exp. 2; Exp. 4 taken 30 min. after Exp. 3
		2	^{2} 6,199	68	360	^{4} 11,624	68	300							
		2	9,748	68	480+										
D. G.	13	2	^{1} 4,041	36	50	^{2} 8,165	48	600+	^{3} 11,875	36	360	14,886	60	300+	Exp. 2 taken right after Exp. 1; Exp. 3 right after Exp. 2; Exp. 5 right after Exp. 4; Exp. 6 right after Exp. 5
		2	^{7} 3,793	40	150	^{5} 8,248	45	180	^{6} 12,044	65	450+				
		2	^{4} 4,370	45	180				^{8} 12,040		360+				
J. D.	12	1½	^{1} 2,844	54	120	^{5} 6,432	80	270	^{6} 8,940	72	420	......	..	...	Exp. 1, 2 and 3 taken on same day at 30 min. intervals; Exp. 4, following day; Exp. 5, 10 min. after Exp. 4; Exp. 6 right after Exp. 5; murmur after Exp. 1; Exp. 8 taken right after Exp. 7; Exp. 9 taken 30 min after Exp. 8; Exp. 10 taken right after Exp. 9
		1½	^{2} 3,218	78	360+	^{7} 4,885	84	120	^{9} 8,660	66	60				
		1½	^{3} 3,154	78	300+	^{8} 6,066	84	270	^{10} 8,472	78	210				
		1½	^{4} 3,402	60	60										
A. H.	10	1½	^{1} 2,907	52	120	^{2} 5,505	72	360	^{3} 7,979	72	390	......	..	...	Exp. 2 taken right after Exp. 1; Exp. 3 taken right after Exp. 2; Exp. 4, 5 and 6 taken on the following day; Exp. 7, 8 and 9 taken one after the other
		1½	^{4} 2,537	58	50	^{5} 5,690	54	420+	^{6} 7,547	72	180				
			^{7} 2,660	72	50	^{8} 5,568	72	390+	^{9} 8,525	84	510+				
J. C.	8	1	^{2} 2,185	55	120	^{1} 3,959	45	240	^{3} 5,449	65	360	......	..	...	Exp. 2 taken right after Exp. 1; Exp. 3 right after Exp. 2; Exp. 4 and 5 taken 1 hour after Exp. 3
			^{4} 2,145	65	240	^{5} 3,918	55	180	^{6} 6,032	60	360				
B. M.	13	2	4,929	66	180	7,620	68	180							
D. H.	13	2	5,953	60	150										
A. J.	12	2	4,931	72	270+	......	..	...	......	..	...	......	..	...	Murmur
L. S.	12	2	2,148	38	40										
R. B.	6	¾	1,354	16	270										
W. T.	14	2	......	..	...	5,294	60	240+							
B. B.	12	2	......	..	...	7,076	48	270							
J. T.	12	2	......	..	...	7,883	90	420							
M. R.	12	2	......	..	...	4,657	48	150+	......	..	...	......	..	...	Discontinued; pain in hand
M. H.	12	2	......	..	...	10,890	90	420+							
A. G.	11	2	......	..	...	7,517	78	480							
G. G.	6	¾	......	..	...	2,164	12	30	......	..	...	......	..	...	Arhythmia and extrasystole
M. F.	14	2	......	..	...	......	..	...	13,842	78	780				
P. O.	13	2	......	..	...	......	..	...	11,365	84	450				
H. A.	10	2	......	..	...	......	..	...	8,155	60	300				
D. Z.	13	2	......	..	...	......	..	...	......	..	...	13,531	72	390	
C. P.	12	2	......	..	...	......	..	...	......	..	...	12,776	55	600+	Arhythmia during first 10″
E. W.	11	1½	......	..	...	......	..	...	......	..	...	13,010	78	240	
A. F.	10	1¼	......	..	...	......	..	...	......	..	...	8,957	34	270	
H. W.	9	1	......	..	...	......	..	...	......	..	...	9,337	78	480+	
Average......	....	....	4,279	62.3	191	6,976	68.5	319.5	9,690	65.8	390	12,083	62.8	(390)	R. B. and G. D. excluded

TABLE 17.—REACTION OF BLOOD PRESSURE TO MEASURED AMOUNTS OF WORK

Subject	Age in Yrs.	Load in Lbs.	1 Minute					2 Minutes					3 Minutes					4 Minutes					Remarks
			Foot-pounds of Work	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	Foot-pounds of Work	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	Foot-pounds of Work	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	Foot-pounds of Work	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	
J. C.	14	2	^{1} 5,838	163	30	54	360	^{5} 9,941	163	40	47	300	^{6}12,465	171	50	69	660+	......	...	..	..	...	Exp. 2 taken 1 hour after Exp. 1; Exp. 3, 45 min. after Exp. 2; Exp. 4, 2 hours after Exp. 3; Exp. 5, 30 min. after Exp. 4
		2	^{2} 5,368	155	20	43	270																
		2	^{3} 4,508	149	50	40	240																
		2	^{4} 5,281	149	5	41	270																
H. B.	14	2	^{1} 6,268	157	5	57	390	^{3}10,788	161	40	55	390	......	...	..	..	...	......	...	..	..	...	Exp. 2 taken 35 min. after Exp. 1; Exp. 3, 2 hours after Exp. 2; Exp. 4, 30 min. after Exp. 3
		2	^{2} 6,199	163	50	58	360	^{4}11,624	173	50	70	510											
		2	9,784	164	10	52	390																
D. G.	13	2	^{1} 4,041	126	5	6	50	^{2} 8,165	154	10	34	270	^{3}11,875	143	20	31	300	^{5}14,886	142	5	27	240	Exp. 2 taken right after Exp. 1; Exp. 3 right after Exp. 2; Exp. 5 right after Exp. 4; Exp. 6 right after Exp. 5
		2	^{7} 3,793	134	40	24	360	^{5} 8,248	132	20	22	300	^{8}12,044	142	5	27	240						
		2	^{4} 4,370	134	10	24	300						^{6}12,040	133	30	23	390						
J. D.	12	1½	^{1} 2,844	157	10	32	180	^{5} 6,432	160	20	46	300	^{6} 8,940	168	5	72	420	......	...	..	..	...	Exp. 1, 2 and 3 taken on same day at 30 min. intervals; Exp. 4, following day; Exp. 5, 10 min. after Exp 4; Exp. 6 right after Exp. 5; murmur after Exp. 1; Exp. 8 right after Exp. 7; Exp. 9, 30 min. after Exp. 8; Exp. 10 right after Exp. 9
		1½	^{2} 3,218	160	10	35	270	^{7} 4,885	164	20	45	330	^{9} 8,660	160	5	51	450						
		1½	^{3} 3,154	158	5	35	300	^{8} 6,066	166	10	45	390	^{10}8,472	158	20	49	300						
		1½	^{4} 3,402	149	20	39	300																
A. H.	10	1½	^{1} 2,907	164	5	50	270	^{2} 5,505	162	5	46	270	^{3} 7,979	155	30	41	390	......	...	..	..	...	Exp. 2 taken right after Exp. 1; Exp. 3 right after Exp. 2; Exp. 4, 5 and 6, the following day; Exp. 7, 8 and 9, one after the other
		1½	^{4} 2,537	157	5	45	270	^{5} 5,690	167	5	56	360	^{6} 7,547	154	10	40	210						
			^{7} 2,660	145	30	36	360	^{8} 5,568	152	10	43	420	^{9} 8,525	148	30	39	390						
J. O.	8	1	^{2} 2,185	131	10	31	360	^{1} 3,959	132	5	32	240	^{3} 5,449	134	10	34	330	......	...	..	..	...	Exp. 2 taken right after Exp. 1; Exp. 3 right after Exp. 2; Exp. 4 and 5, 1 hour after Exp. 3
			^{4} 2,145	126	5	26	300	^{5} 3,918	132	20	32	390	^{6} 6,032	127	5	30	360						
B. M.	13	2	4,929	132	5	29	270	7,620	138	20	42	270											
D. H.	13	2	5,953	122	30	10	120																
C. P.	13	2	4,451	145	30	35	360																
A. J.	12	2	4,931	132	20	32	270	......	...	..	..	...	......	...	..	..	...	......	...	..	..	...	Murmur
L. R.	12	2	2,148	120	10	31	270																
R. B.	6	¾	1,354	111	20	14	270																
W. T.	14	2	......	...	..	..	...	3,294	130	30	21	240											
R. S.	14	2	......	...	..	..	...	7,429	172	30	36	360											
R. B.	12	2	......	...	..	..	...	7,076	147	40	29	270											
J. T.	12	2	......	...	..	..	...	7,883	109	50	15	300											
M. R.	12	2	......	...	..	..	...	4,657	142	10	32	...	......	...	..	..	...	......	...	..	..	...	Discontinued; pain in hand
M. H.	12	2	......	...	..	..	...	10,890	144	40	49	540+											
A. G.	11	2	......	...	..	..	...	7,517	148	20	39	300											
G. G.	6	¾	......	...	..	..	...	2,164	136	30	39	600	......	...	..	..	...	......	...	..	..	...	Arhythmia and extrasystole
M. F.	14	2	......	...	..	..	...	......	...	..	..	...	13,842	166	10	59	390						
P. C.	13	2	......	...	..	..	...	......	...	..	..	...	11,365	134	10	29	360						
H. A.	10	2	......	...	..	..	...	......	...	..	..	...	8,155	174	20	49	270						
D. Z.	13	2	......	...	..	..	...	......	...	..	..	...	......	...	..	..	...	13,531	144	30	46	420	
C. P.	12	2	......	...	..	..	...	......	...	..	..	...	......	...	..	..	...	12,776	154	20	49	330	Arhythmia during first 10″
E. W.	11	1½	......	...	..	..	...	......	...	.	..	...	......	...	..	..	...	13,010	149	5	36	300	
A. F.	10	1¼	......	...	..	..	...	......	...	..	..	...	......	...	..	..	...	8,957	140	10	36	300	
H. W.	9	1	......	...	..	..	...	......	...	.	..	...	......	...	..	..	...	9,337	162	20	61	300	
Aver.	..	..	4,287	145	18.2	36.5	287	6,998	121.2	25.7	39.8	339	9,690	151	17.3	30.1	369	12,083	148	15	42.3	330	

The comparison of the effect of various types of exercise on pulse rate and blood pressure shows their variability. Because of the inconstancy of the pulse rate no definite conclusions can be drawn. The reaction time seems to be more uniform than the increase in the rate. The reaction time is about equal in the staircase test and after one minute ergometer exercise. The pulse rate returns to normal within the shortest period after the dumbbell exercise.

The highest blood pressure rises are observed after sixty full swings of the dumbbells, the staircase exercise and the exhaustive arm exercise in the older children. In the majority of the cases, regardless of the kind of exercise and the amount of work performed, the maximum blood pressure occurs within thirty seconds. The reaction time seems to be more prolonged after the ergometer exercise and the staircase test than after the dumbbell exercises.

Maximum Physical Capacity of Children.—The maximum physical capacity was determined by means of the stationary bicycle, a detailed description of which was given in the first part of this paper. The experiments were limited to boys from 6 to 15 years of age. The muscular work of every boy was determined two or three times on successive days. The results are recorded in Tables 18 to 28. Only those experiments were accepted as accurate in which the child gave evidence of having performed its utmost. The load of work, controlled by manipulation of the screw on the brake and registered on the scale, was 2 pounds for children between 12 and 15 years of age, and from ¾ pound to 1½ pounds for the children aged from 6 to 12. Too great a load makes the riding of the bicycle difficult and joyless, and changes the type of exercise from one of endurance and speed into one of strength. The change of output following a change in load in one and the same subject is clearly demonstrated in Table 30. H. B. was able to produce 2.5 times as much against a load of 2½ pounds as against 3 pounds, and eight times as much against 2 pounds. In the case of H. T. the proportion of physical capacity, using a load of 3, 2½ and 2 pounds was 1, 2½ and 7, respectively. Other examples could be cited to prove the importance of the optimum load for each child. The question might be asked, why should the load not be decreased to a minimum if the difference in output evidently depends on the quantity of resistance? Two pounds was chosen for the optimum for the older boys because at that resistance the subject did not complain of difficulty in turning the wheel and any load under 2 pounds would have considerably prolonged the experiment. With the optimum load the children rode the bicycle for on an average of about fifteen minutes.

TABLE 18.—EFFECT OF MAXIMUM AMOUNT OF WORK IN FOOT-POUNDS ON PULSE AND SYSTOLIC BLOOD PRESSURE. AGE 6 YEARS

Subject	Age in Years	Weight in Pounds	Height in Inches	Foot-Pounds of Work	Pulse					Systolic Blood Pressure							Remarks
					Before Exercise	After Exercise				Before Exercise Mm.	After Exercise						
						Maximum Reading	Time of Maximum Reading, Sec.	Rise	Reaction Time, Sec.		First Reading, Mm.	Time of First Reading, Sec.	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	
B. D.	6	53.5	47¾	^{2} 11,960	89	...	..	..	600+*	95	132	5	132	5	37	360	*Pulse 100 at 600″
				^{1} 11,775	78	...	..	..	330+*	95	132	5	132	10	37	270	*Pulse 96 at 330″
G. H.	6	56	48	^{1} 7,107	105	...	..	..	420+*	119	152	5	154	5	35	390	*Pulse 114 at 420″
				^{2} 6,544	92	...	..	..	180	109	138	5	148	10	39	300	
A. T.	6	57	49	^{2} 6,994	120	...	..	..	120	106	122	5	132	20	17	300	
				^{1} 5,829	126	...	..	..	90	108	134	10	134	10	26	300	
M. E.	6	44.5	46	6,135	95	...	..	..	270+*	102	121	5	123	10	21	300	*Pulse 108 at 270″
E. B.	6	47.5	46½	5,540	95	...	..	..	390+*	91	127	5	133	30	18	360	*Pulse 108 at 390″
5 cases, 8 determinations	6	51.7	47 9/20	7,736	100	...	..	..	270+	103.1	132.3	5	134.4	12.5	30.3	322	

TABLE 19.—EFFECT OF MAXIMUM AMOUNT OF WORK IN FOOT-POUNDS ON PULSE AND SYSTOLIC BLOOD PRESSURE. AGE 7 YEARS

Subject	Age in Years	Weight in Pounds	Height in Inches	Foot-Pounds of Work	Pulse					Systolic Blood Pressure							Remarks
					Before Exercise	After Exercise				Before Exercise Mm.	After Exercise						
						Maximum Reading	Time of Maximum Reading, Sec.	Rise	Reaction Time, Sec.		First Reading, Mm.	Time of First Reading, Sec.	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	
U. W.	7	61.5	51	^{2} 19,503	102	...	..	..	390+*	110	130	5	132	35	22	330	*Pulse 120 at 390″
				^{1} 11,793	110	...	..	..	420+*	111	125	5	137	15	26	330	*Pulse 120 at 420″
C. J.	7	50.75	46¾	^{1} 15,807	100	...	..	..	540+*	94	107	10	129	30	35	330	*Pulse 130 at 540″
				^{2} 12,699	96	...	..	..	450+*	86	112	10	116	35	30	330	*Pulse 106 at 450″
C. K.	7	58	47½	^{1} 15,510	80	...	..	..	360+*	98	125	10	129	15	31	390	*Pulse 100 at 360″
				^{2} 13,206	80	...	..	..	450+*	95	116	5	124	15	29	390	*Pulse 110 at 450″
T. S.	7	58	47½	^{2} 14,312	81	...	..	..	300+*	94	108	10	123	25	29	270	*Pulse 108 at 300″
				^{1} 10,954	90	...	..	..	330	98	121	10	125	30	27	420	
M. B.	7	53.5	49¾	^{2} 13,914	86	...	..	..	390+*	94	128	5	128	5	34	300	*Pulse 100 at 390″
				^{1} 13,416	82	...	..	..	390	94	129	5	129	5	35	300	
H. S.	7	45	46¾	^{2} 12,869	96	...	..	..	570+*	96	132	10	132	10	36	†	*Pulse 108 at 570″
				^{1} 11,293	110	...	..	..	210	93	126	10	126	10	33	390	†Bl. Pr. 110-114 from 210-600″
L. D.	7	54.75	48	^{2} 10,978	84	...	..	..	570+*	94	128	5	133	20	39	300†	*Pulse 96 at 570″
				^{1} 9,430	105	...	..	..	240	105	128	5	153	40	48	300	†Bl. Pr. 101 from 300-540″
H. P.	7	58.5	48½	^{2} 10,440	96	...	..	..	450+*	99	114	10	115	10	16	330	*Pulse 132 at 450″
				^{1} 9,922	98	...	..	..	420+*	98	118	10	118	10	20	300	*Pulse 135 at 420″
E. B.	7	51	46¾	^{2} 8,584	100	...	..	..	510	81	95	5	114	30	33	420†	*Pulse 130 at 390″
				^{1} 7,294	115	...	..	..	390+*	106	139	5	139	5	33	270	†Bl. Pr. 93 from 420-600″
S. R.	7	47.25	46¼	^{2} 6,600	90	...	..	..	180	81	108	5	109	15	28	330	
				^{1} 6,229	92	...	..	..	300+*	85	116	5	116	5	31	390	*Pulse 110 at 300″
10 cases, 20 determinations	7	53.8	47 $^9/_{10}$	11,738	94.6	...	..	..	390+	95.6	120.2	5	126.4	18.2	30.7	353	

TABLE 20.—EFFECT OF MAXIMUM AMOUNT OF WORK IN FOOT-POUNDS ON PULSE AND SYSTOLIC BLOOD PRESSURE. AGE 8 YEARS

Subject	Age in Years	Weight in Pounds	Height in Inches	Foot-Pounds of Work	Pulse					Systolic Blood Pressure							Remarks
						After Exercise					After Exercise						
					Before Exercise	Maximum Reading	Time of Maximum Reading, Sec.	Rise	Reaction Time, Sec.	Before Exercise Mm.	First Reading, Mm.	Time of First Reading, Sec.	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	
I. P.	8	76.75	52½	^{2} 32,458	85	200	5	115	360+*	114	141	5	149	20	35	390	*Pulse 120 at 360″
				^{1} 17,684	107	...	..	..	540+*	113	140	5	149	10	36	420	*Pulse 115 at 540″
J. C.	8	57.5	48	^{1} 24,651	96	156	5	60	600+*	101	128	5	134	20	33	390	*Pulse 102 at 600″
				^{3} 20,003	96	168	10	72	600+*	102	118	5	129	10	29	300	*Pulse 114 at 600″
				^{2} 18,966	96	180	5	84	480+*	108	126	5	130	20	28	180	*Pulse 108 at 480″
H. B.	8	79.5	52¾	^{2} 21,663	90	160	5	70	360+*	102	142	5	142	5	40	330	*Pulse 105 at 360″
				^{1} 15,205	98	...	..	..	360	107	134	10	136	10	29	240	
M. S.	8	60.25	49¾	^{3} 19,588	96	168	5	72	480+*	89	105?	10	122	90?	33	390†	*Pulse 120 at 480″
				18,384	108	180	5	72	360+*	101	119	5	123	20	22	180	†Bl. Pr. 100 from 390-600″
				10,072	108	144	5	36	570	99	105	10	116	35	17	210	*Pulse 120 at 360″
G. S.	8	60.25	48	^{3} 19,380	96	156	5	60	510+*	97	119	5	125	20	28	360	*Pulse 114 at 510″
				^{1} 13,363	90	168	5	78	510+*	98	134	5	138	20	36	300	*Pulse 108 at 510″
				^{2} 11,911	96	168	5	72	360+*	101	118	10	130	20	19	210	*Pulse 126 at 360″
J. B.	8	55.75	48½	^{2} 18,380	80	...	..	..	570+*	99	120	5	128	20	29	270†	*Pulse 100 at 570″ †Bl. Pr. 107 from 270-600″
				^{1} 16,766	76	...	..	..	570+*	104	116	10	119	60	15	240†	*Pulse 84 at 570″ †Bl. Pr. 105-109 from 240-600″
O. F.	8	55	49	^{2} 17,247	102	...	..	..	600+*	93	111	10	123	30	30	330†	*Pulse 126 at 570″ †Bl. Pr. 110 from 330-600″
				^{1} 11,165	90	...	..	..	270+*	102	129	10	133	40	31	330	*Pulse 115 at 270″
J. J.	8	64.25	51½	^{2} 16,102	96	144	5	48	300+*	98	117	5	126	10	30	210	*Pulse 108 at 300″
				^{1} 12,259	108	...	..	..	.....	99	118	5	128	20	29	180	
				^{3} 11,039	96	156	5	60	540*	95	122	5	122	5	27	420	*Pulse 108 at 540″
W. P.	8	59	49	^{1} 15,670	96	...	..	..	330+*	112	136	5	143	30	31	270	*Pulse 126 at 330″
				^{2} 14,236	102	...	..	..	510+*	113	143	10	151	20	38	390	*Pulse 120 at 510″
M. G.	8	71.75	53½	^{2} 14,802	95	...	..	..	240+*	87	103	10	107	30	19	300	*Pulse 110 at 240″
				^{1} 13,840	82	...	..	..	330+*	96	113	5	127	30	31	270	*Pulse 110 at 330″
10 cases, 24 determinations	8	64	49.3	16,870	94.8	165.3	5	69.1	510+	101.2	123	5	126.2	21.9	28.9	293	

TABLE 21.—EFFECT OF MAXIMUM AMOUNT OF WORK IN FOOT-POUNDS ON PULSE AND SYSTOLIC BLOOD PRESSURE. AGE 9 YEARS

Subject	Age in Years	Weight in Pounds	Height in Inches	Foot-Pounds of Work	Pulse					Systolic Blood Pressure							Remarks
						After Exercise					After Exercise						
					Before Exercise	Maximum Reading	Time of Maximum Reading, Sec.	Rise	Reaction Time, Sec.	Before Exercise Mm.	First Reading, Mm.	Time of First Reading, Sec.	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	
M. B.	9	65.5	53	^{2} 38,215	90	...	..	..	600+*	108	130	10	130	10	38	300	*Pulse 108 at 600″
				^{1} 24,320	92	...	..	..	600+*	108	123	5	123	5	15	270	*Pulse 114 at 600″
H. G.	9	59	50½	^{2} 36,893	86	...	..	..	520+*	100	113	10	116	20	16	360	*Pulse 106 at 520″
				^{1} 20,869	104	...	..	..	450+*	107	133	10	140	40	33	360†	*Pulse 112 at 450″ †Bl. Pr. 117 at 360″; to remain there
H. W.	9	77.5	55½	^{1} 33,906	90	144	5	54	450	104	128	5	128	5	24	150	Load 1 pound
				^{2} 21,603	84	...	..	..	420+*	103	143	5	143	5	40	210	*Pulse 96 at 420″; load 1¼ pound
H. G.	9	61.5	52¼	29,460	96	...	..	..	600+*	103	130	5	130	5	27	330	*Pulse 100 at 600″
J. B.	9	79	56	^{2} 28,890	96	...	..	..	360+*	105	124	5	124	5	19	150	*Pulse 120 at 360″
				^{1} 12,325	108	...	..	..	600+*	120	140	10	149	20	29	240†	*Pulse 120 at 600″ †Bl. Pr. 127 at 240″; 127-132 from 240-600″
C. H.	9	67	53¼	^{1} 26,270	90	168	5	78	600+*	112	131	15	133	10	21	210	*Pulse 102 at 600″
				^{2} 19,378	96	...	..	..	390	93	130	5	130	5	37	270	
J. G.	9	58.5	51½	^{2} 26,165	81	...	..	..	420+*	88	108	5	122	20	36	300	*Pulse 120 at 420″
				^{1} 17,772	90	...	..	..	450	98	122	5	133	20	35	240	
R. O.	9	68.75	53½	^{1} 20,998	102	...	..	..	510+*	98	138	5	138	5	40	570	*Pulse 126 at 510″
				^{2} 16,937	116	...	..	..	390+*	101	135	20	131	10	34	360	*Pulse 125 at 390″
H. W.	9	61.5	59	^{2} 17,724	90	...	..	..	420+*	101	129	10	133	40	32	300	*Pulse 102 at 420″
				^{1} 12,610	88	. .	..	..	420+*	110	130	5	143	30	33	210	*Pulse 100 at 420″
M. L.	9	57	51	^{2} 15,251	84	...	..	..	570+*	91	103	10	119	30	28	270†	*Pulse 108 at 570″ †Bl. Pr. 98-101 from 270-600″
				^{1} 12,577	87	...	..	..	570+*	91	113	5	129	30	38	300†	*Pulse 102 at 570″ †Bl. Pr. 98-103 from 300-600″
10 cases, 19 determinations	9	65.25	54	21,608	93.2	...	..	..	510+	102	132	5-10	131	16.6	30.4	282	

TABLE 22.—EFFECT OF MAXIMUM AMOUNT OF WORK IN FOOT-POUNDS ON PULSE AND SYSTOLIC BLOOD PRESSURE. AGE 10 YEARS

Subject	Age in Years	Weight in Pounds	Height in Inches	Foot-Pounds of Work	Pulse					Systolic Blood Pressure							Remarks
						After Exercise					After Exercise						
					Before Exercise	Maximum Reading	Time of Maximum Reading, Sec.	Rise	Reaction Time, Sec.	Before Exercise Mm.	First Reading, Mm.	Time of First Reading, Sec.	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	
H. S.	10	74	55¼	^{2} 57,331	93	...	..	..	510+*	93	112	5	119	20	26	270	*Pulse 108 at 510″
				^{1} 45,752	96	192	5	96	390+*	107	127	5	127	5	20	300	*Pulse 144 at 390″
J. H.	10	104.5	56¼	^{2} 40,202	93	...	..	..	600+*	107	142	5	147	30	40	420	*Pulse 108 at 600″
				^{1} 30,378	100	180	5	80	600+*	106	142	5	142	5	36	360	*Pulse 120 at 600″
H. A.	10	67	53¼	^{1} 36,444	100	180	5	80	600+*	117	158	5	168	30	51	360	*Pulse 114 at 600″; murmur
				^{2} 29,517	87	...	...	..	450+*	119	143	10	158	30	39	300	*Pulse 120 at 450″
L. C.	10	63.75	53¾	^{2} 35,531	85	...	..	..	330+*	97	115	20	119	30	22	240	*Pulse 125 at 330″
				^{1} 24,337	110	...	..	..	390+*	100	121	20	121	20	21	210	*Pulse 140 at 390″
A. H.	10	60	50¼	^{2} 28,750	90	100	5	90	600+*	107	154	5	154	5	47	330	*Pulse 120 at 600″
				^{1} 24,319	·106	192	5	86	600+*	118	149	10	161	30	43	360	*Pulse 120 at 600″
G. C.	10	67	52¾	^{2} 22,590	108	...	..	..	480+*	92	122	5	127	10	35	270†	*Pulse 132 at 480″ †Bl. Pr. remains at 102; other children presesnt
				^{1} 21,611	105	...	..	..	600+*	100	120	15	124	40	24	240	*Pulse 126 at 600″
F. C.	10	71	55	^{2} 22,469	84	...	..	..	480+*	99	148	5	148	5	49	390	*Pulse 108 at 480″
				^{1} 17,679	90	...	5	..	600	114	148	5	157	30	46	420	
A. F.	10	64	51	^{2} 20,933	90	144	10	54	390+*	101	128	5	128	5	27	210	*Pulse 120 at 390″
				^{1} 20,275	96	...	..	..	600+*	103	126	10	137	40	34	240	*Pulse 108 at 600″
C. J.	10	91	53¾	^{1} 9,898	108	168	5	60	510+*	109	142	5	143	5	34	210	*Pulse 120 at 510″
				^{2} 7,318	102	156	5	54	300	106	148	5	150	5	42	180	
9 cases, 18 determinations	10	73.6	53½	27,518	96.8	164	5	75	510+	105.3	135.8	5	140.6	19.2	35.3	296	

TABLE 23.—EFFECT OF MAXIMUM AMOUNT OF WORK IN FOOT-POUNDS ON PULSE AND SYSTOLIC BLOOD PRESSURE. AGE 11 YEARS

Subject	Age in Years	Weight in Pounds	Height in Inches	Foot-Pounds of Work	Pulse					Systolic Blood Pressure							Remarks
					Before Exercise	After Exercise				Before Exercise Mm.	After Exercise						
						Maximum Reading	Time of Maximum Reading, Sec.	Rise	Reaction Time, Sec.		First Reading, Mm.	Time of First Reading, Sec.	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	
P. H.	11	89.5	57½	[1] 57,123	86	...	..	..	510+*	103	135	5	150	25	47	330	*Pulse 126 at 510″
				[2] 48,103	87	...	..	..	390	103	128	5	138	10	35	360	
G. D.	11	70	52¾	[2] 54,552	78	...	..	..	510+*	107	132	5	137	20	25	390	*Pulse 108 at 510″
				[1] 36,164	80	...	..	..	.....	119	142	5	149	30	30	450	
S. B.	11	75	55½	[2] 40,296	96	...	..	..	420+*	103	121	10	125	60	22	390	*Pulse 132 at 420″
				[1] 35,773	91	...	..	..	570+*	103	129	15	129	15	26	240	*Pulse 108 at 570″
H. R.	11	73.75	52¾	[1] 37,235	90	...	..	..	510+*	96	130	10	131	20	35	390	*Pulse 114 at 510″
				[2] 35,418	91	...	..	..	510+*	98	108	5	117	20	19	360	*Pulse 126 at 510″
A. G.	11	80	54¾	33,831	86	...	..	..	600+*	111	137	5	137	5	26	330	*Pulse 102 at 600″
P. M.	11	82	54¾	[2] 32,100	97	...	..	..	390+*	103	124	5	128	10	25	270	*Pulse 102 at 390″
				[1] 30,974	101	...	..	..	.....	115	140	5	142	15	37	240	
E. R.	11	92.5	60½	31,706	100	...	..	..	120	101	126	5	132	10	31	270	Bicycle too small; no dyspnea
E. W.	11	60	52¼	[2] 27,574	90	...	..	..	510+*	100	140	10	150	35	50	540	*Pulse 114 at 510″; tremor
				[1] 17,056	102	192	5	90	540+*	108	142	5	151	50	43	390	*Pulse 108 from 330-540″
V. B.	11	74	55¼	[2] 24,918	86	...	..	..	600+*	91	122	5	122	5	31	300†	*Pulse 102 at 600″ † Bl. Pr. 95 at 300″; 97-203 from 300-600″; dyspnea after exercise very prolonged
				[1] 23,015	87	...	..	..	600+*	96	131	5	137	50	43	240†	*Pulse 102 at 600″ †Bl. Pr. 104-109 from 240-600″
A. F.	11	146	62¼	[2] 19,040	96	180	5	84	400+*	117	158	5	158	5	47	†	*Pulse 108 at 13 min.
				[1] 13,820	108	190	30	84	600+	110	158	30	167	50	57	300	†Bl. Pr. 125 at 200″; 22 and 23 after 13 min.
10 cases, 18 determinations	11	84.3	54⅘	33,261	91.8	...	..	..	510+	110.4	133.5	5	138.8	18.6	35.5	350	

TABLE 24.—EFFECT OF MAXIMUM AMOUNT OF WORK IN FOOT-POUNDS ON PULSE AND SYSTOLIC BLOOD PRESSURE. AGE 12 YEARS

Subject	Age in Years	Weight in Pounds	Height in Inches	Foot-Pounds of Work	Pulse					Systolic Blood Pressure							Remarks
						After Exercise					After Exercise						
					Before Exercise	Maximum Reading	Time of Maximum Reading, Sec.	Rise	Reaction Time, Sec.	Before Exercise Mm.	First Reading, Mm.	Time of First Reading, Sec.	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	
J. D.	12	68	48½	^{1} 48,048	96	192	5	96	600+*	113	140	5	158	40	45	570	*Pulse 114 at 600″
				^{2} 40,275	84	168	5	84	600+*	113	148	5	158	20	45	510†	*Pulse 108 at 600″ †Presence of principal might have delayed drop of blood pres.
H. R.	12	75	56½	^{2} 56,881	90	216	5	126	600+*	103	138	5	144	50	41	420	*Pulse 120 at 600″
				^{1} 40,481	90	192	5	102	420+*	101	138	5	155	30	54	390	*Pulse 120 at 420″
A. M.	12	109	61½	^{3} 44,837	96	180	5	84	600+*	136	188	5	188	5	52	330	*Pulse 120 at 600″
				^{1} 37,740	72	180	5	108	450+*	129	135	5	155	30	27	210†	*Pulse 126 at 450″ †Bl. Pr. below normal at 240″, 116 at 450″
				^{2} 26,240	90	156	10	66	900+*	132	169	20	169	20	37	150	*Pulse 120 at 900″, 90 at 30 minutes
D. G.	12	100	58¼	^{1} 44,514	115	180	5	65	420+*	115	126	5	138	30	23	210	*Pulse 132 at 420″
				^{2} 30,139	112	168	5	56	540+*	112	130	5	132	5	20	210	*Pulse 115 at 540″; murmur
J. T.	12	76	55½	^{1} 30,709	84	...	..	..	360+*	102	124	5	124	5	22	180	*Pulse 126 at 360″; Exp. 1 against 1½ pounds
				^{2} 12,622	104	...	..	..	420+*	100	121	10	130	30	30	360	*Pulse 120 at 420″; Exp. 2 against 1¾ pounds
T. B.	12	89	54¾	^{1} 24,299	84	156	10	72	480+*	102	107	15	127	50	25	240	*Pulse 96 at 480″
				^{2} 29,224	90	156	5	66	390+*	100	115	5	134	20	34	300	*Pulse 102 at 390″
J. B.	12	88.5	58	^{2} 28,711	66	...	..	..	600+*	98	129	5	136	20	43	360	*Pulse 82 at 600″
				^{1} 14,836	60	...	..	..	600+*	99	124	10	132	20	33	270	*Pulse 78 at 600″
M. S.	12	81.5	..	25,452	87	...	..	..	600+*	97	120	10	133	50	36	450	*Pulse 120 at 600″
A. J.	12	74	57¼	^{1} 22,970	84	156	5	72	600+*	115	152	5	152	5	37	270	*Pulse 96 at 600″; murmur
				^{2} 20,853	66	132	5	66	540+*	116	140	5	147	20	31	210	*Pulse 84 at 540″
B. B.	12	62.5	52¾	^{2} 18,407	84	156	10	72	540+*	109	155	5	159	10	50	390	*Pulse 108 at 540″
				^{1} 14,069	96	180	5	84	540+*	112	148	5	149	5	36	240	*Pulse 108 at 540″
A. G.	12	80.5	60	^{1} 16,904	84	168	30	84	240+*	107	134	30	140	60	33	240+†	*Pulse 108 at 240″ †Bl. Pr. 114 at 240″ (one of first Exp. made)
				^{2} 14,667	84	168	5	84	480+*	107	128	5	145	40	38	270	*Pulse 96 at 480″
M. R.	12	74	56	16,790	108	132	30	24	240	108	152	30	152	30	44	450	
12 cases, 23 determinations	12	84.1	56	29,216	87	171.8	5	81.6	600+	110	136.8	5	144.2	24.3	36.2	323	M. R. excluded

TABLE 25.—EFFECT OF MAXIMUM AMOUNT OF WORK IN FOOT-POUNDS ON PULSE AND SYSTOLIC BLOOD PRESSURE. AGE 13 YEARS

Subject	Age in Years	Weight in Pounds	Height in Inches	Foot-Pounds of Work	Pulse					Systolic Blood Pressure							Remarks
					Before Exercise	After Exercise				Before Exercise Mm.	After Exercise						
						Maximum Reading	Time of Maximum Reading, Sec.	Rise	Reaction Time, Sec.		First Reading, Mm.	Time of First Reading, Sec.	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	
C. J.	13	95	59	^{4} 70,735	96	180	5	82	600+*	95	133	5	146	40	51	450	*Pulse 120 at 420-720″
				^{3} 49,954	96	192	5	96	390+*	96	148	5	148	5	52	300	*Pulse 120 at 390″
				^{2} 42,196	96	192	5	96	600+*	105	151	3	151	5	46	240	*Pulse 126 at 600″
				^{1} 28,339	96	168	5	72	390	94	150	10	150	10	56	300	
A. P.	13	112.5	62	69,354	108	180	10	72	1,020+	113	146	10	146	10	33	240	
L. W.	13	124.5	66	^{2} 62,534	102	180	5	78	1,560+*	110	162	5	162	5	52	300	
				^{1} 35,571	84	168	10	84	600+*	105	145	20	147	20	42	240	
L. R. S.	13	83	60¾	46,953	96	120	15	24	180	91	120	10	120	10	29	300+*	*Bl. Pr. 101 at 300″; uncomfortable; discont.
M. W.	13	100	67½	^{2} 42,807	96	180	5	84	420+*	112	154	5	158	20	48	210	*Pulse 114 at 420″
				^{1} 30,321	84	156	10	72	300+*	115	141	20	141	20	28	210	*Pulse 108 at 300″
B. M.	13	80	56	^{2} 42,293	90	180	5	90	390+*	98	120	5	130	50	32	390	*Pulse 114 at 390″; Exp.2 against 1⅓ pounds
				^{1} 14,281	96	180	10	84	480+*	100	130	10	137	30	37	480+†	*Pulse 115 at 480″; Exp.1 against 2 pounds †Bl. Pr. 116 at 480″
D. Z.	13	99.5	61	40,247	108	192	5	84	420+*	95	111	5	126	10	31	240	*Pulse 132 at 570″
E. L.	13	75	55½	30,374	76	192	10	116	360+*	96	128	10	128	10	32	210	*Pulse 132 at 360″
P. C.	13	92.5	60¾	^{2} 29,041	108	192	5	86	360*	108	126	5	126	5	21	210	*Pulse 108 at 360″
				^{1} 29,021	96	204	10	108	600	108	137	10	137	10	26	420	
M. S.	13	85	59¾	26,955	108	180	10	72	420	98	125	10	128	20	30	420	
C. S.	13	90	60¼	24,764	78	180	10	102	1,020+*	106	150	10	154	20	50	600†	*Pulse 96 at 17 min., 78 at 42 min.; murmur †Bl. Pr. 115 at 330″; remained there until 570″; 110 at 600″
B. C.	13	88.5	60¼	15,733	108	180	5	72	420	105	124	10	133	40	28	390	
D. H.	13	90	59¼	^{1} 10,627	84	156	10	72	300+*	104	142	20	142	20	38	300	*Pulse 108 at 300″; neurotic boy
				^{2} 8,434	90	168	5	78	420+*	102	134	5	138	20	36	330	*Pulse 108 at 420″
13 cases, 21 determinations	13	86.4	60.6	38,749*	85	178	5-10	82	390+	103	137	5-10	140	18.1	38	300	*Last 2 cases excluded

TABLE 26.—EFFECT OF MAXIMUM AMOUNT OF WORK IN FOOT-POUNDS ON PULSE AND SYSTOLIC BLOOD PRESSURE. AGE 14 YEARS

Subject	Age in Years	Weight in Pounds	Height in Inches	Foot-Pounds of Work	Pulse					Systolic Blood Pressure							Remarks
						After Exercise					After Exercise						
					Before Exercise	Maximum Reading	Time of Maximum Reading, Sec.	Rise	Reaction Time, Sec.	Before Exercise Mm.	First Reading, Mm.	Time of First Reading, Sec.	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	
H. B.	14	118	63	[2] 86,500	78	144	40	66	270+*	113	165	20	167	20	54	300	*Pulse radial, 84 at 270″; exp. made 1½ hours after exp. listed below
				[1] 77,378	84	132	10	48	180+*	116	158	10	158	10	42	330	*Pulse 94 at 180″
				[3] 66,506	96	192	5	96	360+*	109	146	5	149	10	40	240	*Pulse 132 at 360″
R. G.	14	122	63¼	83,082	84	144	30	60	300	122	172	30	172	30	50	420	
J. C.	14	93	60¾	[1] 76,290	72	140	30	68 ?	*	113	141	30	145	60?	32	180	*Pulse 96 at 210″; one of the first exp. made
				[2] 51,404	84	192	5	108	1,020+*	111	143	10	149	20	40	180	*Pulse 108 at 17 min.
W. T.	14	76	58	[2] 55,346	80	156	5	76	600+*	109	138	5	138	5	29	270	*Pulse 108 at 600″
				[1] 40,276	78	156	10	78	600+*	108	142	5	146	10	38	330	*Pulse 108 at 600″
A. F.	14	85.5	58¾	[2] 51,441	96	180	5	84	660+*	99	132	5	132	5	33	330	*Pulse 114 at 660″
				[1] 50,310	90	156	10	66	690*	96	133	10	134	10	38	360	*Pulse 97 at 690″
J. B.	14	109	63	[1] 46,705	108	168	10	60	960*	116	127	10	136	20	20	420	*Pulse 126 at 960″; murmur after exercise
				[2] 45,511	96	192	5	96	510+*	123	150	5	159	50	59	330	*Pulse 120 at 510″
M. H.	14	75	56	37,202	74	180	5	116	600+*	103	139	5	148	20	36	270 or 300	*Pulse 114 at 600″
M. S.	14	120	65	[2] 36,035	102	180	5	80	600+*	121	172	5	172	5	51	330	*Pulse 114 at 10-15 min.
				[1] 23,452	96	192	10	96	600+*	129	167	10	167	10	32	420	*Pulse 114 at 14 min.; murmur
E. R.	14	97	59	25,865	100	180	10	80	600+*	102	138	10	142	20	40	330	*Pulse 108 at 600″; 102 at 12 min.
C. H.	14+	93.5	59¾	[1] 25,141	81	168	10	87	600+*	113	156	10	158	10	45	330	*Pulse 96 at 660″
				[2] 18,314	102	180	10	68	420*	118	150	20	155	30	37	270	*Pulse 108 at 420-720″
F. L.	14	109.5	61	24,952	102	180	5	78	540+*	114	147	5	153	40	39	420	*Pulse 132 at 540″; murmur
H. P.	14	98	63	20,730	81	168	10	87	540+*	93	132	20	132	20	39	240	*Pulse 108 at 540″
M. K.	14	97.5	58½	[2] 20,579	96	192	5	96	600+*	109	144	5	153	30	44	360	*Pulse 120 at 600″; murmur
				[1] 15,165	108	180	10	93	450	103	142	10	144	20	43	240	
M. F.	14	85	59½	8,248	90	168	20	78	780	109	166	10	166	10	57	390	*Pulse 102 at 450″
14 cases, 23 determinations	14	97.7	60⅗	42,049	86	170.5	5-10	81.3	540+	106.5	145.2	5-10	147.4	18.4	41	313	

TABLE 27.—EFFECT OF MAXIMUM AMOUNT OF WORK IN FOOT-POUNDS ON PULSE AND SYSTOLIC BLOOD PRESSURE. AGE 15 YEARS

Subject	Age in Years	Weight in Pounds	Height in Inches	Foot-Pounds of Work	Pulse					Systolic Blood Pressure							Remarks
						After Exercise					After Exercise						
					Before Exercise	Maximum Reading	Time of Maximum Reading, Sec.	Rise	Reaction Time, Sec.	Before Exercise Mm.	First Reading, Mm.	Time of First Reading, Sec.	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	
D. F.	15	...	..	108,762	96	192	5	96	300+	113	142	5	146	10	33	240	*Pulse 132 at 300″
H. F.	15	116	63	68,701	96	192	10	96	300+*	116	150	20	150	20	34	210	*Pulse 96 at 570″; subject collapsed at 2d experiment, having done 123,599 ft. lbs.
P. L.	15	110	62½	45,820	110	192	5	82	960+*	128	159	5	166	20	38	360	*Pulse 120 at 16 min.; 144 at 360″
				25,886	96	180	5	84	540+*	129	153	5	168	60	39	270	*Pulse 108 at 540″; 126 at 360″
3 cases, 4 determinations	15	113	63	62,295	99	189	5	90	300+	124	154	5	158	27.5	36	270	

TABLE 28.—EFFECT OF MAXIMUM AMOUNT OF WORK IN FOOT-POUNDS ON PULSE AND SYSTOLIC BLOOD PRESSURE. AGES 15 TO 6 YEARS

Number of Cases	Age in Years	Weight in Pounds	Height in Inches	Foot-Pounds of Work	Pulse					Systolic Blood Pressure							Remarks
						After Exercise					After Exercise						
					Before Exercise	Maximum Reading	Time of Maximum Reading, Sec.	Rise	Reaction Time, Sec.	Before Exercise Mm.	First Reading, Mm.	Time of First Reading, Sec.	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.	
3 cases, 4 determinations	15	113	63	62,295	99	189	5	90	300+	124	154	5	158	27.5	36	270	
14 cases, 23 determinations	14	97.7	60.6	42,049	86	170.5	5-10	81.3	540+	106.5	145.2	5-10	147.4	18.4	41	313	
13 cases, 21 determinations	13	86.4	60.6	38,749*	85	178	5-10	82	390+	103	137	5-10	140	18.1	38	300	*Two cases excluded
12 cases, 23 determinations	12	84.1	56	29,216	87	171.8	5	81.6	600+	110	136.8	5	144.3	24.3	36.4	323	Case of M. R. excluded
10 cases, 18 determinations	11	84.3	55.8	33,261	91.8	...	..	..	510+	110.4	133.5	5	138.8	18.6	35.5	350	
9 cases, 18 determinations	10	73.6	53.5	27,518	96.8	164	5	75	510+	105.3	135.8	5	140.6	18.1	35.3	297	
10 cases, 19 determinations	9	65.25	54	21,608	93.2	...	..	..	510+	102	132	5-10	131	16.6	30.4	282	
10 cases, 24 determinations	8	64	49.3	16,870	94.8	165.3	5	69.1	510+	101.2	123	5	126.2	21.9	28.9	293	
10 cases, 20 determinations	7	53.8	47.9	11,738	94.6	...	..	..	390+	95.6	120.2	5	126.4	18.2	30.7	353	
5 cases, 8 determinations	6	51.7	47.45	7,736	100	...	..	..	270+	103.1	132.3	5	134.4	12.5	30.3	322	

Close observation of physical signs of exertion was made throughout the experiment. Flushing, breathlessness, slight and severe perspiration were recorded (Fig. 4) as soon as they appeared. Fatigue of the legs usually set in after the first two or three minutes of exercise but disappeared soon after. It reappeared on prolonged exercise. Toward the end of the ride, the majority of children complained about muscular fatigue, only a few complained of precordial distress. The degree of breathlessness, subjectively, was not in proportion to the amount of work nor the state of exhaustion. Of 200 experiments on 101 subjects, eight developed a murmur at the end of exercise. The murmurs were short in duration, systolic in time and heard only at the apex. Four of the murmurs were cardiopulmonary, while the other four were uninfluenced by respiration. They all disappeared within ten minutes after cessation of work.[10]

The fourth column in Tables 18 to 28 represents the maximum output in foot pounds of children between 6 and 15 years of age. It can be seen that the results vary in different children of the same age and are also inconstant for one and the same child at different times. This applies only to children past 8 years of age. Under 8, the variability is only about 1,000 foot pounds. In children above 8, no two experiments result in the same quantity of work, although the same external conditions, as time of day and relation to food, were carefully observed in successive experiments. Repetition usually increased a child's output. Will power, depending on the mood, seemed to play a great part in the total amount of work. The individual variance amounts to less than 1,000 foot pounds for children of 6 years to about 1,300 foot pounds at 7 years, 5,000 foot pounds at 8 years, on an average of 8,000 foot pounds from 9 to 11 years and more than 10,000 foot pounds from 11 to 15 years. Generally speaking, only about 31 per cent. of all children examined showed an individual variation of less than 2,000 foot pounds. It must be borne in mind that the results obtained are only of comparative value.

Relationship Between Physical Output and Certain Physical Factors.—What factors determine the physical capacity of a person? Is the efficiency in children proportionate to their height and weight? Does good physical development expressed in the circumference of the chest and thigh assure one of greater physical endurance? Do the advocates of physical training justly assume that training is followed by increased muscular efficiency?

---

[10] The formula used for calculating the amount of foot pounds per minute is as follows: number of revolutions per minute $\times$ load $\times \frac{63.025''}{4 \times 12} \times 2\pi$: $\frac{63.025''}{4 \times 12}$ represents the length of the beam.

Effect of Height and Weight on Physical Capacity.—The heights and the weights of all the children were grouped into one inch and five pound divisions, respectively. The weights are but relative, since the children were not undressed. Table 29 B shows a steady and almost constant increase of physical capacity in children from 45 to 51 inches in height. Such a constancy in increase is not apparent in children taller than fifty-one inches. Table 29 A shows a similar relationship between weight and working capacity.

Up to 9 years of age the physical capacity seems to be in proportion to the height and weight. In older children, however, the physical capacity is not influenced by these two factors.

Effect of Physical Development on Physical Capacity.—In Figure 5 can be noted the relationship between the amounts of work and the circumference of the chest. Each dot represents the arithmetical means of the results of two or three experiments in the same child. The straight line is the actual curve of the arithmetical means of the maximum output. The dotted line represents the theoretical curve obtained by smoothing the humps which are seen in the straight line. These curves show a definite relation between the circumference of the chest and maximum physical capacity.

TABLE 29.—Relation Between Weight and Capacity for Work in Normal Children, Age 6 to 15 Years

A			B		
Number of Cases	Weight in Pounds	Amount of Work in Foot-Pounds	Number of Cases	Height in Inches	Average Work in Foot-Pounds
3	125–121	53,179	6	63	58,770
2	120–116	36,475	3	62	43,520
1	115–111	53,897	3	61	34,756
4	110–106	36,496	5	60	36,621
1	105–101	10,126	5	59	33,609
5*	100– 96	32,292	3	58	34,503
6	95– 91	37,179	5	56	36,817
4	90– 86	37,513	11	55	35.417
6	85– 81	35,509	9	54-53	27,711
7	80–176	37,711	7	52	30,470
9	75– 71	33,457	7	51	20,956
7	70– 66	31,099	6	50-49	15,566
4	65– 61	17,533	7	48	11,490
12	60– 56	16,116	5	47-45 incl.	6,680
6	55– 51	12,039			
5	50– 45	6,034			

Also in Figure 6 we find a definite relation between the circumference of the thigh and the amount of work in foot pounds. The curve running through the dots is a smoothed one based on the arithmetic averages of maximum output at 1 cm. measurements of the thigh.

Effect of Training on Physical Capacity.—To determine the effect of training on the capacity for work the subjects were divided into two groups: those who knew how to ride a bicycle and those who did not. It is, of course, obvious that such a comparison must be lacking in accuracy since the degree of training was not taken into account. It was found, in general, that children who rode a bicycle surpassed in physical capacity those who did not. Bicycle riding increased the physical efficiency 30 per cent. at 8 years, 20 per cent. at 9 years, 48 per cent. at 10 years, 7 per cent. at 11 years, 42 per cent. at 12 years, 53 per cent. at 13 years, and 36 per cent. at 14 years.

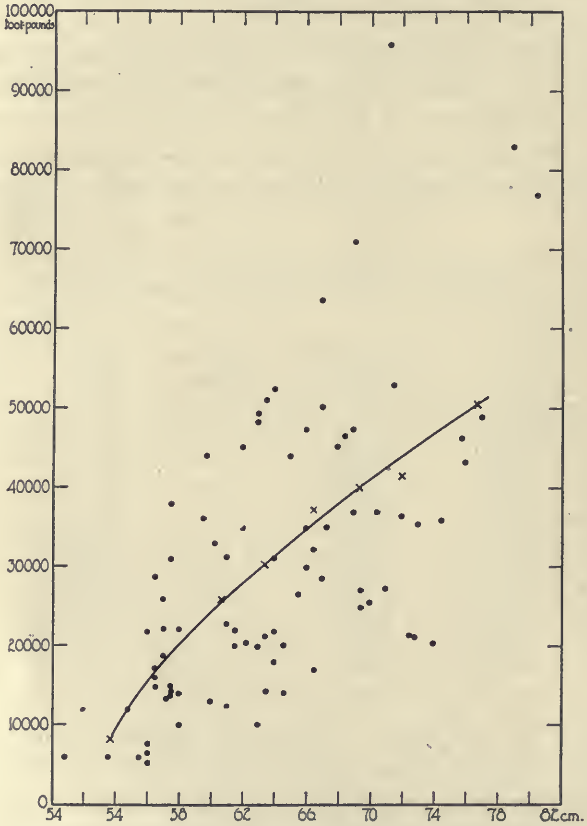


Fig. 5.—Relationship between circumference of chest and maximum physical capacity.

Effect of Vital Capacity on Physical Capacity.—The vital capacity of the children examined ranged from 1,000 to 3,550 c.c. Figure 7 shows the close relation between vital capacity divided into groups of 300 c.c. and the maximum physical output. In Figure 7 the straight line represents the output in foot pounds intersecting corresponding points of vital capacity at 300 curve intervals. The dotted line is the theoretic smoothed curve.

The effect of exercise on vital capacity was also determined in six children from 9 to 14 years of age. Each of the subjects had to perform his utmost on the ergometer on three successive days, and on the fourth day the subject was allowed to run up three flights of stairs as fast as possible, three times in succession. In every instance the vital capacity showed neither a decrease nor an increase over the vital capacity taken each time right before exercise. This is significant in the presence of marked dyspnea and fatigue.

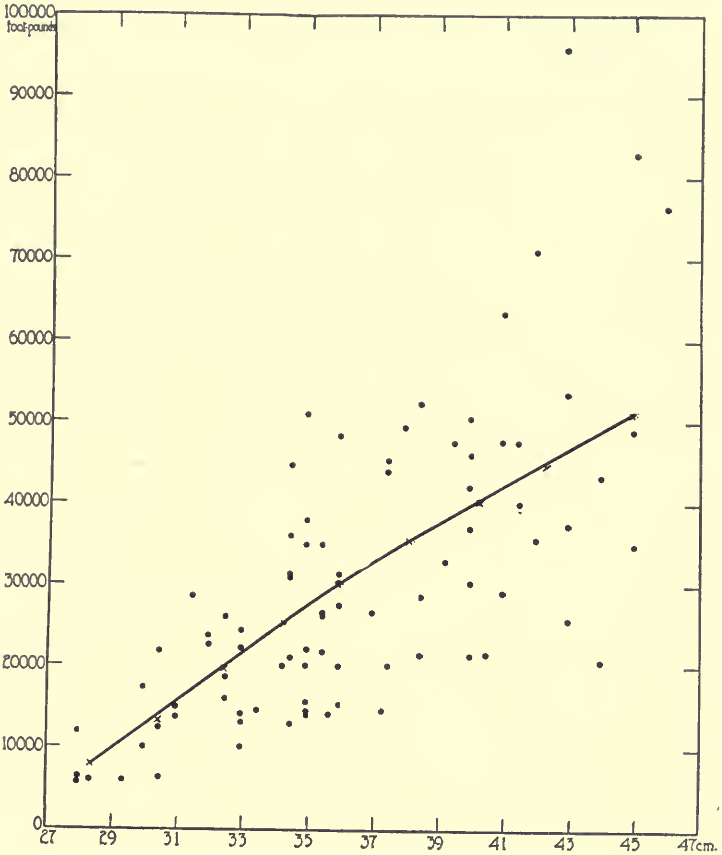


Fig. 6.—Relationship between circumference of thigh and maximum physical capacity.

Effect of Age on Physical Capacity.—A most definite relation exists between physical capacity and age. Figure 8 shows the increase of maximum working capacity with age. The curve represents a straight line slightly broken at 10 years of age. Calculations revealed that the relationship between age and maximum physical work can be expressed in two empirical formulas, one pertaining to children from 6 to 10 years of age, the other applicable to children from 11 to 14 years.

Formula I: Maximum physical output (age from 6 to 10 years) = 1,000 (5.45 age — 25.3).

Formula II: Maximum physical output (age from 11 to 14 years) = 3,000 × age.

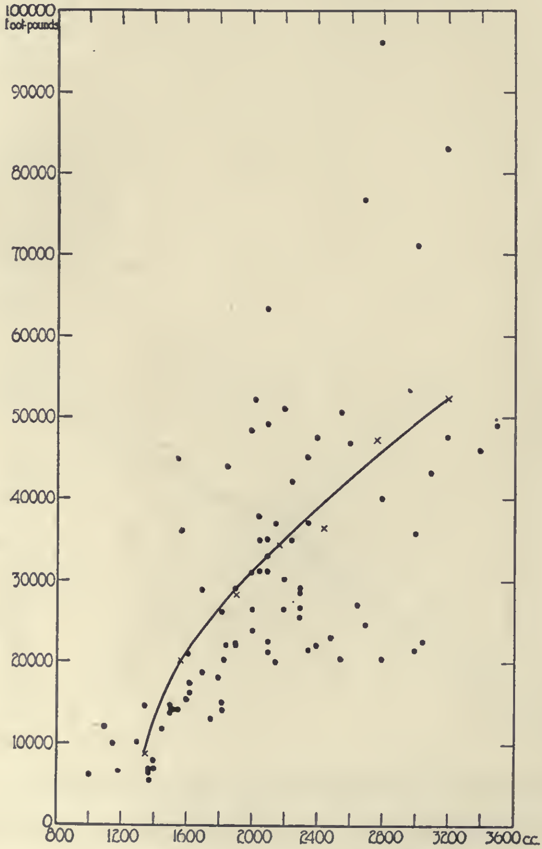


Fig. 7.—Relationship between vital capacity and maximum physical capacity.

Effect of Maximum Amount of Work on the Pulse Rate.—The first reading of the pulse rate was taken within from five to ten seconds after cessation of exercise. During the first minute counts of the pulse rate were repeated at intervals of ten seconds (five seconds being devoted for each reading). From the second minute on, the pulse rate was recorded in one-half minute periods for ten minutes. The maximum reading in column 7 of Tables 18 to 28 is the equivalent of the first reading taken, multiplied by twelve. It, therefore, does not represent the true rate of the pulse for the entire first minute. The true rate for the first minute can be obtained by adding up all the readings (about six) taken during the first minute. This was only carried out in subjects with a maximum reading above 165. This figure was taken as the upper limit because of the claim of other investigators who considered a rate above 160 as indicative of myocardial insufficiency. Forty-nine children, aged from 8 to 15 years, showed a maximum reading above 165 per minute. It was found that of the forty-nine children with a maximum reading above 165, only twenty-one had an actual pulse rate of 165 and over during the first minute following the cessation of work. Of thirteen boys, aged 14, four had a pulse rate from 165 to 169 (I. C., A. F., C. H. and M. K.), one of 171 (M. K.) and another of 180 (M. S.). In seven of the 13 year old boys a pulse rate over 165 was found: From

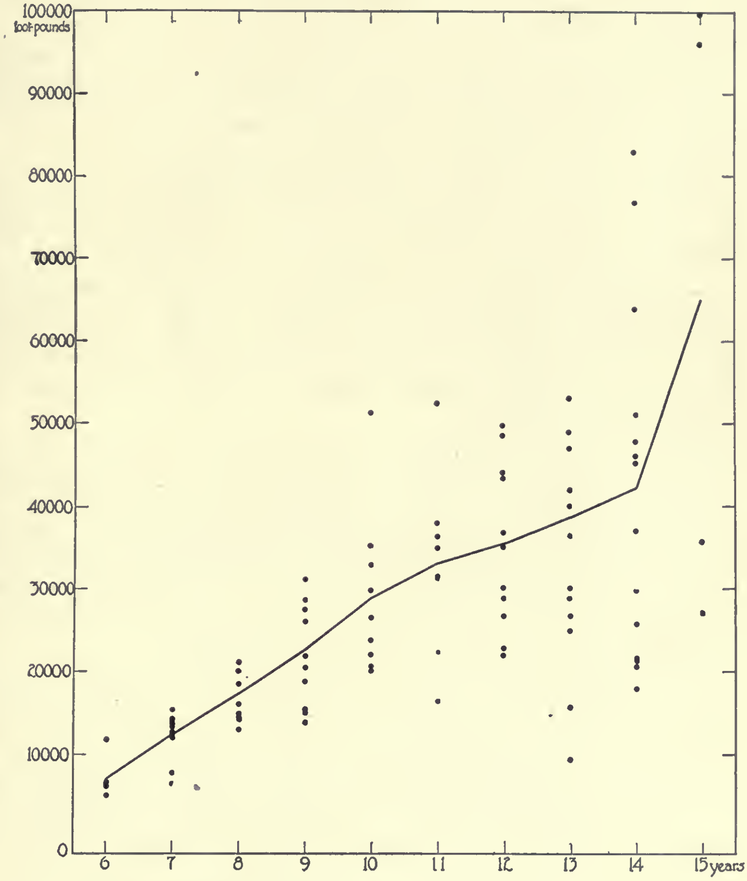


Fig. 8.—Relationship between age and maximum physical capacity.

165 to 169 in three cases; three with a rate of from 170 to 175 and one with a pulse of 184 (E. L.). Among the 12 year old children there were two with a pulse rate from 165 to 169 (I. B., A. M.), one with a pulse of 170 (D. E.) and another boy with a pulse rate as high as 193 (H. R.). Two boys, aged 11, had counts of 172 (E. W.) and 178 (A. F.). One 10 year old boy (A. H.) had a pulse rate of 180 and another one (T. P.), aged 8, had the same rate. None of these children showed any signs of overexertion, such as nausea, fainting or dull heart sounds. These results would indicate that a pulse rate above 160 after exercise is not incompatible with a normal myocardium.

The rise in pulse rate after exercise varies from as low as forty-eight to as high as 116. The increase in the pulse rate does not seem to be parallel with the increase in work in exhaustive exercises.

For instance, H. B., aged 14, showed the highest rise (96) in the experiment in which he performed 20,000 foot pounds less than in the experiment that caused his pulse rate to rise only seventy-eight beats. C. T., aged 13, had a maximum rise of twelve beats lower in an experiment 28,000 foot pounds higher than in a following experiment. More instances could be cited to show that a decrease in work is not necessarily followed by a decrease in the rise of the pulse rate and vice versa.

In general, there is a slight average increase of the rise with age (Table 28). The reaction time of the pulse is of no clinical value. In the earlier experiments it was noticed that practically none of the pulse rates returned to normal within ten minutes after cessation of work. In two experiments the reaction time of the pulse was thirty and thirty-five minutes, respectively. Therefore, the determination of the pulse rate was omitted in the later experiments.

Effect of Maximum Amount of Work on the Systolic Blood Pressure.—As referred to previously, the blood pressure cuff was kept partially inflated during the last three seconds of exercise so as to obtain the first reading as soon as experimentally possible after stopping. The majority of the first blood pressure readings were, therefore, taken within five seconds, a smaller number within ten seconds.

Rise of Blood Pressure After Exercise.—A comparison of the increases in systolic blood pressure obtained in the same subject after different amounts of maximum work revealed the interesting fact that in only about one half of all the experiments was there a higher rise after larger amounts of work. The most striking examples are P. L., aged 15, who after accomplishing 45,820 foot pounds had a rise in blood pressure of 20 mm. and after 25,886 foot pounds of 60 mm.; I. B., aged 14, had a rise of 20 mm. after 46,705 foot pounds

TABLE 30.—EFFECT OF LOAD ON WORKING CAPACITY

Subject	Age in Years	Weight in Lbs.	Height in Inches	Load in Lbs.	Foot-Pounds of Work	Pulse					Blood Pressure						
							After Exercise					After Exercise					
						Before Exercise	Maximum Reading	Time of Maximum Reading, Sec.	Rise	Reaction Time, Sec.	Before Exercise	First Reading, Mm.	Time of First Reading, Sec.	Maximum Reading, Mm.	Time of Maximum Reading, Sec.	Rise, Mm.	Reaction Time, Sec.
H. B.	14	118	63	3	9,684	102	180	5	78	480+	112	150	5	164	40	52	450
				2½	23,826	102	180	10	78	660	107	144	5	153	30	46	600
				2	66,506	96	192	5	96	360+	109	146	5	149	10	40	240
C. I.	13	95	59	3	7,530	90	144	10	54	420	96	159	10	159	10	63	420
				2½	17,438	96	168	10	72	600+	95	148	10	157	30	62	480
				2	49,954	96	192	5	96	390+	96	148	5	148	5	52	300
B. M.	13	80	56	2	14,281	96	180	5	90	480+	106	130	10	137	30	39	390
				1¾	42,293	90	180	5	90	390+	98	120	5	130	50	32	390

against a rise of 59 mm. after 45,511 foot pounds. The conclusion is justified that an increase in work is not necessarily accompanied by a proportionate increase in the blood pressure. The average rise amounted to 30 mm. for children from 6 to 9 years of age, from 35 to 41 mm. for the older children. The highest rise observed was 57 mm. in a boy aged 11; the minimum was 16 mm. in a boy aged 7.

Time of Maximum Reading of Blood Pressure.—Because of the recent work of Barringer[11] and Wilson, in which they claim that a secondary maximum rise of blood pressure sixty seconds or later after cessation of exercise indicates "temporary heart insufficiency," a thorough investigation into the time of the maximum reading after exhaustive exercise was made.

It is to be noted in Table 31 A that the majority of the subjects exhibit the maximum blood pressure at from five to thirty seconds. In general, 88 per cent. show the maximum blood pressure reading within thirty seconds after exercise. Twelve per cent. of the highest readings occur between thirty and sixty seconds. In only 1.1 per cent. is the reading highest at sixty seconds and later. Of the total number there were only four that could possibly be considered "delayed rises." One experiment in which the maximum reading was at sixty seconds (A. G., aged 12 years) was incomplete, only two readings having been obtained, one at thirty seconds and the other at sixty seconds. (M. S., aged 8) had a maximum reading at ninety seconds, the accuracy of which was doubtful. The two remaining subjects with a maximum rise definitely at sixty seconds were S. B., aged 11, and J. B., aged 8. The latter had the maximum reading at twenty seconds after having accomplished 18,300 foot pounds and a "delayed rise" after only 16,700 foot pounds. In neither instance did he show any subjective signs of "temporary heart insufficiency." The same is true of subject S. B. The results of this present investigation cannot be taken as a confirmation of Barringer's and Wilson's findings. Wilson tabulated sixty-five experiments with dumbbells. With the exception of four determinations the increase in blood pressure was proportionate to the increase in work. The time of the maximum reading also corresponded to the amount of work performed that is, the greater the quantity of work, the later the maximum reading. Readings at sixty seconds and after occured only after more severe exercise (from 2,000 to 3,000 foot pounds). Wilson found "delayed rises" in 21 per cent. of the experiments. It seems logical to assume that if she obtained

---

[11] Barringer, T. B.: Studies of the Heart's Functional Capacity as Estimated by the Circulatory Reaction to Graduated Work, Arch. Int. Med. **17**:363 (March) 1916; **17**:670 (May) 1916. Studies of the Heart's Functional Capacity, Arch. Int. Med. **20**:329 (Sept.) 1917.

"delayed rises"—after her subjects performed about 2,000 foot pounds, that we should also have obtained similar results since our subjects performed from 50,000 to 60,000 foot pounds to the point of real exhaustion.

Reaction Time of Blood Pressure.—Wilson also claims that the reaction time of the systolic blood pressure is proportionate to the amount of work in almost all of her experiments. This is not in agreement with Tables 18 to 28. Comparison of the results obtained shows definitely that in 51 per cent. of the ergometer experiments the reaction time of the same subject is higher after larger amounts of work; that in 32 per cent. the reaction time is shorter though the work performed is higher (e. g. with subject B. M., aged 13, the reaction time is 390 seconds after 42,000 foot pounds and 480 seconds after 14,000 foot pounds.) In 14 per cent. of the experiments the reaction time is the same, though the subjects performed different amounts of work. I. C., aged 14, showed a reaction time of 180 seconds, though the work performed was 76,000 and 51,000 foot pounds, respectively.

TABLE 31.—A. TIME OF MAXIMUM READING AFTER EXHAUSTIVE EXERCISE

Sec.	Age									No. of Cases
	14 Yrs.	13 Yrs.	12 Yrs.	11 Yrs.	10 Yrs.	9 Yrs.	8 Yrs.	7 Yrs.	6 Yrs.	
5	3	4	5	3	7	7	2	4	2	37
10	7	6	10	3	1	3	4	6	4	44
20	7	7	6	6	2	4	10	3	1	48
30	3	1	5	2	6	3	5	5	1	31
40	1	2	2	0	2	2	1	2	0	12
50	1	1	3	3	..	..	..	..	..	8
60	1?	..	1?	1	..	..	1	..	..	2 and 2?
90	..	..	..	..	..	..	1?	..	..	1?
No. cases	22	21	31	18	18	19	23	20	8	
Aver.	18.4	19	18.2	24.6	19.1	16.5	18.2	18.5	15	

Average = 19; probable error = 3.33; coefficient variability = 0.26.

B. REACTION TIME OF BLOOD PRESSURE AFTER EXHAUSTIVE EXERCISE

Sec.	15 Yrs.	14 Yrs.	13 Yrs.	12 Yrs.	11 Yrs.	10 Yrs.	9 Yrs.	8 Yrs.	7 Yrs.	6 Yrs.	15-6 Yrs.
150	0	0	0	1	0	0	2	0	0	0	3
180	0	2	0	1	0	1	0	3	0	0	7
210	1	0	4	4	0	3	3	3	0	0	18
240	1	3	4	2	2	2	1	1	0	0	17
270	1	3	0	3	2	1	2	2	2	1	17
300	0	1	4	1	1	2	3	3	4	4	23
330	0	7	1	1	2	1	1	2	6	0	21
360	1	2	0	2	2	3	2	1	0	2	15
390	0	1	2	2	4	1	0	3	4	1	18
420	0	4	2	1	0	2	0	2	1	0	12
450	0	0	1	2	1	0	0	0	0	0	3
480	0	0	0	0	0	0	0	0	0	0	..
510	0	0	0	1	0	0	0	0	0	0	1
540	0	0	0	0	1	0	0	0	0	0	1
570	0	0	0	1	0	0	1	0	0	0	1
Delayed time	0	0	2	1	3	1	4	4	3	0	18

Average = 310; probable error = ±15.16; coefficient of variability = 7.25.

In 3 per cent. of all readings the same amount of work in two repeated experiments was accompanied by different reaction times. The conclusion must be drawn that a direct ratio between the reaction time of the blood pressure and the increase of work is found in only a slight majority of subjects. The longest reaction time was 600 seconds in a boy, aged 13 (C. S.), and the shortest, 150 seconds (H. W., aged 9, J. B., aged 9, and A. M., aged 12). Statistical calculation shows the average to be 310.3 ± 15.16. The coefficient of variability equals 7.25. There is practically no change in reaction time with a change in age (Table 31 B).

Comparison of the Blood Pressure and Pulse Rate During and After Exercise.—Very few investigations of the physiology during exercise on adults have been made and none at all in children. In this work the readings were begun right after the onset of exercise and continued every minute throughout the entire experiment.

Pulse During Exercise (57 cases; Table 31).—The pulse showed an increase almost immediately after the beginning of the ride, remaining at a plateau for most of the period during exercise and usually descending toward the end of the ride. The pulses in six carefully studied cases showed that in one case the pulse rate immediately after cessation of exercise was twelve beats higher than during, in two the same and in the three remaining lower after than during exercise.

Blood Pressure During Exercise (Table 31; 75 cases).—The blood pressure showed a curve similar to the pulse rate except that its initial rise was slower. In eleven cases (26.6 per cent.) the blood pressure during exercise was on the average 10 mm. higher than after exercise. In forty-four cases (58.6 per cent.) it was the same and in twenty cases (26.6 per cent.) the systolic pressure during exercise was lower than the blood pressure immediately after.

CONCLUSIONS

1. Pulse rate and systolic blood pressure in normal children of school age: (1) The pulse rate in the standing posture is invariably higher than in the lying posture, the ratio being 1.15. (2) The systolic blood pressure in the lying posture is invariably higher than in the standing posture; the ratio of the pressure in the lying posture to that in the standing equals 1.11. (3) The ratio between the systolic blood pressure in the lying and the standing positions is about equal to the ratio between the pulse rate in the standing and lying positions.

2. Effect of exercise on the systolic blood pressure and on the pulse rate in normal children of school age: (1) All forms of exercise produce an increase in the pulse rate and the blood pressure, the increase depending mainly upon the type of exercise. (2) Neither

the amount of exercise nor the speed determine the time of maximum reading. (3) In the majority of cases the increase of the pulse rate and the blood pressure as well as the reaction time of the blood pressure are in direct proportion to the speed and the amount of work performed. (4) Height and weight do not influence the maximum physical output. (5) The maximum physical output is in direct relationship to the age, circumference of the chest, circumference of the thigh and the vital capacity. (6) Two formulas have been computed for calculating the maximum physical output with age as the basis. Formula I (applying to children from 6 to 10 years of age): 1,000 (5.45 age — 25.3). Formula II (applying to children from 11 to 14 years of age): 3,000 × age. (7) In exhaustive exercises on the ergometer, the increase of the pulse rate varies from 48 to 116 beats irrespective of age. It is not necessarily parallel with the amount of work performed. (8) In exhaustive exercise, the rise of blood pressure is proportional to the increase in work in about 50 per cent. of the experiments. (9) The average rise in blood pressure after exhaustive exercise equals 31 mm. in children aged from 6 to 9 years and 35 to 41 mm. in older children. The maximum rise equals 57 mm.; the minimum rise equals 16 mm. (10) Eighty-eight per cent. of all the determinations made show the maximum reading of the systolic blood pressure within thirty seconds, 12 per cent. between thirty and sixty seconds. In only two cases of the entire series is there a true delayed rise. In our experiments delayed rises do not occur after exhaustive exercise nor as the result of "temporary heart insufficiency." (11) The reaction time of the pulse is too long to be of any clinical value, very few pulse rates returning to normal within ten minutes. (12) In general, the reaction time of the systolic blood pressure increases with an increase in work. There are, however, exceptions to this conclusion. The average reaction time after exhaustive work equals 310 seconds, with a probable error of ± 15. The longest reaction time found is 600 seconds; the shortest is 150 seconds.

We want to express our thanks to Dr. R. E. Scammon, professor of anatomy, University of Minnesota, for his help with the statistics of the paper.

CELIAC DISEASE *

ROOD TAYLOR, M.D.
MINNEAPOLIS

Samuel Gee described celiac disease in 1888. In 1921, Reginald Miller,[1] in compiling a retrospect of the literature concerning it, mentioned about fifty papers, but even his excellent bibliography is not complete. A study of this literature makes it evident that, in general, the accounts of celiac disease, celiac infantilism, Herter's infantilism, intestinal infantilism, acholia, pancreatic infantilism, pancreatic insufficiency and of a certain type of chronic intestinal indigestion agree fairly well in the description of a condition which we can hypothetically consider to be one specific morbid entity.

The disease has never been recognized in a breast fed infant. In its typical form it is always chronic. The children suffering with it are undersize and underweight. The roentgen ray shows delayed skeletal development and the muscles are small, soft and weak. This weakness is most noticeable in the legs. The abdomen is distended. The stools are voluminous, gray, greenish or brown, at times porridgy, at times containing much mucus and at times being liquid. They are usually foul, but may be rancid. Acute attacks of diarrhea occasionally occur; but for the major part of the time the patient has no more than two or three stools daily. These attacks of diarrhea usually occur after feeding carbohydrates or following the decomposition of retained bowel contents.

The fat content of the feces is greatly increased. This fat is usually fairly well split. The calcium outflow is likewise increased, and this increase over the normal is greater than is accounted for by the amount of fatty acid, volatile acid, or phosphate present in the stools.

The rate of metabolism is slightly diminished. There is usually some degree of secondary anemia and the spleen is often moderately enlarged. The mental ability of these children is usually far in advance of their physical powers. They are apt to be hypochondriacal. The most frequent complications are scurvy, tetany, edema and purpura.

The reports of fifteen necropsies are cited in the literature. At least ten of these must be thrown out of consideration, as there is no

---

* Received for publication, Sept. 13, 1922.

* From the Children's Clinic of Minneapolis.

* Read at the Thirty-Fourth Annual Meeting of the American Pediatric Society held at Washington, D. C., May 1-3, 1922.

[1] Miller: Brit. J. Child. Dis. **18**:11-17. (References included in Miller's Bibliography are not mentioned here.)

evidence that they were cases of celiac disease. Of the remaining five cases, three showed small celled infiltration and fibrosis, particularly about the pancreatic ducts, and one also showed fatty degeneration of the liver. I doubt whether more than one[2] of these represents the usual type of celiac disease. At any rate it is fully as probable that the lesions found followed long continued indigestion with its irritative bowel contents and abnormal bacterial flora as that they were causative of the disease. In the other two cases which are clearly typical of celiac disease, the necropsy showed no changes which could in any way account for the symptoms present. In particular it is to be noted that in neither of the two were pathologic changes found in the liver, duodenum or pancreas.

It has been suggested that the disease follows acute or subacute disorders of digestion and that it is at least associated with the abnormal presence of bacteria, such as *B. bifidus, B. infantilis,* and *B. coli* in the upper intestine. According to this view, the disease results from an infection either of the bowel contents or of the intestine, with a resultant defect in absorption. Other hypotheses as to etiology include chronic infection with one of the other type of dysentery bacillus; deficient or defective pancreatic secretion; deficient or defective secretion of bile; vitamin deficiency; and an overgrowth of proteolytic bacteria in the bowel contents which can be corrected by a change in diet.[3] Defective fat splitting seems to have played a prominent rôle in certain cases, but this was often temporary and, as a rule, the characteristic stools seem to have resulted not from indigestion per se, but from a defect in absorption which may be due to the same causes that produce the abnormal intestinal flora.

The present report is based on a study of seven cases, the cardinal features of which agree with those described as characteristic of celiac disease. Abstracts of their records and of the data gleaned from each appear as an appendix to this paper.

During the development and establishment of the disease, six of the seven patients received an unsuitable diet. In five cases the diet was largely cow's milk and carbohydrates, the principal form in which the latter was administered being potato. Eggs were given freely in three cases. One child subsisted for two years on Horlick's malted milk and bread and butter. Only one of the seven children was given a well balanced and variegated diet. In this instance, the disease developed after an attack of bronchopneumonia. In a second patient, the disease followed pertussis. Another child developed a condition similar to Banti's disease, and had all her digestive symptoms exaggerated following a hemorrhage from the bowel. A fourth child was, in spite of some indigestion, thriving fairly well; but developed all the symptoms of celiac disease immediately after an attack of chickenpox. Pertussis occurred six months after establishment of the disease in the fifth child, but apparently did not make the condition noticeably worse. In the sixth case there is no history of infection, and in the seventh case it is almost certain that there had been none.

---

[2] Porter: Am. J. Dis. Child. **6**:65 (July) 1913. Arroga and Vinas: Arch. de méd. d. enf. **3**:402.

[3] Porter, Morris and Meyers: Am. J. Dis. Child. **18**:254 (Sept.) 1919.

In the light of these cases, it would seem that the best way to produce celiac disease is to feed a susceptible child throughout his second year on a diet rich in milk, fat, and potato, and then to subject him to some parenteral infection.

The roentgen ray, in each instance, showed a dilated atonic colon. The livers were uniformly small; in two cases the roentgen-ray shadow of the liver occupied only the area covered by two ribs and an interspace. The spleen was removed from one patient and showed hypertrophy of the connective tissue stroma, similar to that found in Banti's disease.

Free hydrochloric acid was absent in all of the five cases in which the stomach contents were examined. In two cases anacidity still persists in spite of marked improvement. In two others, including the one in which the spleen was removed, free hydrochloric acid is now present in the gastric juice. The test meal used consisted of toast and meat broth.

From three patients we obtained duodenal juice which contained bile salts, amylase, trypsin and bilirubin. In the only patient of the three whose symptoms were acute, it also contained large amounts of urobilinogen. As this patient was not anemic, and had received no toxic drugs, the presence of urobilinogen in the duodenal juice must mean diffuse liver pathology. It is of interest to note that Bahr encountered urobilinuria in several cases of sprue.[4]

In one case, which went on to exitus, leucin and tyrosin were found in the urine three months before death. This finding, likewise, indicates extensive disease of the liver.

Quantitative examinations of the fat in the stools of four of the patients were made by Dr. F. B. Kingsbury of the University of Minnesota. In the patient whose spleen was removed, the fat utilized before splenectomy was 72 per cent.; following splenectomy it had risen to 90 per cent. The per cent. of fat excreted unsplit before splenectomy was 36 per cent. and after splenectomy it was unchanged. In the patient whose duodenal juice contained urobilinogen, 72 per cent.

---

[4] Bahr: A Report on Researches in Sprue in Ceylon, 1912-1914, quoted by Bauman: Arch. Int. Med. **28**:475 (Oct.) 1921.

of the excreted fat was split. In two cases 81 and 89 per cent. respectively, of the fat was utilized. In one case 11 per cent. of the excreted fat was unsplit, in the other 12 per cent.

In all cases it was found possible to alter the color and odor of the stool by changes in the diet.

Agglutination tests with the Flexner and Shiga types of dysentery bacillus were made in four cases, with negative results.

In support of the hypothesis that there is a causal relationship between the bad feeding and parenteral infection at the onset and disturbed gastric and hepatic functioning at the height of the disease are: (1) that the gastric juice of the infant aged 1 or 2 years normally contains less hydrochloric acid than does that of the adult; (2) that cow's milk has a much higher buffer value than breast milk;[5] (3) that parenteral infections often produce gastric anacidity; (4) that extensive but often unrecognized and usually transitory injury to the liver frequently occurs during bacteremias, and (5) [Whipple's[6] finding] that carbohydrate far more than protein or fats tends to protect the liver against toxic injury.

Marked carbohydrate intolerance had forced most of these patients to a protein and fat diet before they came under my care. At that time they were usually somewhat anemic; but their color was sallow as well as pale. Their livers were small, their intestines relaxed and distended and their stools foul, gray, fatty and voluminous. Up until one year ago the basis of our diet in these cases was protein milk to which other foods were gradually added. When acute exacerbations occurred we would resort to breast milk. For the past year we have begun treatment with a solution of Karo corn syrup flavored with orange juice. We have continued this for two or three days and have then gone over to Marriott's skimmed lactic acid milk to which we have added the curd of an equal quantity of skimmed milk.[7] With this we have been able, as a rule, to give 7 per cent. of Karo corn syrup. The initial improvement has been striking; the most noticeable feature being the striking change in the color of the skin, which has become pink and white instead of sallow. Coincidentally, the child's liver has become much larger. On this diet alone, two children, one aged 2 years and the other 4 years, have become able to walk. The first gained 13 pounds in nine months, the latter, 7 pounds in a year. The latter child grew 2 inches taller and began to walk before any addition was made to her diet. She was not receiving cod liver oil.

---

5. Marriott: Brit. J. Child. Dis. **18**:129-135.
6. Davis and Whipple: Arch. Int. Med. **22**:612 (Nov.) 1918.
7. Marriott: Proc. Washington University Med. Soc., October, 1921.

On protein milk the stools remained foul. On the lactic acid milk with added curd, they have not been foul. Formerly on the protein milk relapses were frequent. On the lactic acid milk they have occurred twice in one patient and not at all in two others who have come under treatment more recently and in whom greater care has been taken to prevent accumulation within the intestine. Furthermore, these patients tolerate more soluble carbohydrate with the skimmed lactic acid milk than they do with the protein milk.

To the lactic acid milk and curd we have slowly added such foods as scraped lean beef, gelatin, flourball porridge, toast, powdered spinach, emulsified cod liver oil, cream and egg yolk. Orange or lemon juice has been administered regularly in every case.

I have employed bile salts and dilute hydrochloric acid without producing any improvement but so far have had no experience in the use of pancreatic extracts nor secretin. In the three patients who were transfused because of anemia the procedure was followed by some digestive improvement.

In all cases we have found it necessary to give enough liquid petrolatum three times daily to secure regular bowel movements.

This discussion of treatment should not close without mention of the remarkable effect produced on the appearance of the stools by splenectomy in the patient who had developed Banti's disease. Three weeks after the operation they appeared altogether like normal stools. They were darker, firmer and contained much less fat than before, although the diet was precisely the same. In fact, the child became so constipated that a three day stool specimen could be obtained only by the use of enemas.

It appears that there are four points to be considered in successful dietary treatment: (1) In recognition of the achlorhydria, to use soured milk and fruit acids; (2) to supply readily absorbable carbohydrate primarily for its good effect on the liver; (3) to wait patiently for months on a high protein intake before adding starches and fats, and (4) to prevent fecal accumulations which can undergo bacterial decomposition.

SUMMARY

In all seven patients the disease was preceded by a long period of bad feeding, or by a parenteral infection, or by both.

Gastric achlorhydria was present in the five cases in which the stomach contents were examined.

The liver was found smaller than normal in every case. As further evidence of the presence of liver pathology there was in one case a complicating Banti's disease; in another case leucin and tyrosin were present in the urine, and in a third case the duodenal juice contained a pathologic pigment.

Finally, I wish to emphasize the remarkable therapeutic efficacy of lactic acid milk and corn syrup.

ABSTRACTS OF CASE RECORDS

CASE 1.—*History.*—P. H., boy, born January, 1917, was breast fed for about one year. After seven months he began to get cow's milk (from 1 to 1½ quarts daily), cereals, bread, potato and egg. When 16 months old he began to vomit occasionally and then was noticed to be getting thinner and weaker.

Examination.—At 18 months he was a flabby fairly well nourished boy with a distended abdomen. The stool was voluminous, foul, grayish and fatty.

Treatment.—This child was transfused; was fed on various diets, the most successful of which was breast milk, but he gradually failed and died at the age of 31 months.

Comment.—There was never much vomiting; but at times great anorexia. He showed the common complications of tetany and edema. His liver became very small and three months before his death the urine contained leucin and tyrosin. In this case there is no evidence of a parenteral infection; but the child had been grossly overfed, particularly with cow's milk. Attention is called to the very small liver and to the presence of leucin and tyrosin in the urine three months before death.

CASE 2.—*History.*—D. B., girl, born January, 1918, was breast fed ten months. She was well until August, 1919, when she had bronchopneumonia followed by a slow convalescence during which her abdomen was first noticed to be distended. In July, 1920, she had an acute diarrhea; since then she has had a continuous intestinal indigestion and has gradually lost strength.

Examination.—In October, 1921, the principal examination findings were: height, 35½ inches; weight, 26 pounds; small soft muscles; distended abdomen; liver edge palpable 1.5 cm. below the costal margin; spleen not palpable. The stools were voluminous, foul and fatty. Quantitative examination of the fat content of the stools showed that 35.5 per cent. of the weight of the dried feces was fat. Of this fat, 28 per cent. was in the form of neutral fat and 72 per cent. in the form of fatty acid and soaps.

Blood: Hemoglobin, 80 per cent.; red blood cells, 4,120,000; white blood cells, 9,850. Differential count: polymorphonuclears, 54 per cent.; lymphocytes, 43 per cent.; transitionals, 2 per cent.; eosinophils, 1 per cent.

Gastric Juice: Repeated examinations showed an absence of free hydrochloric acid. Duodenal juice was obtained from this patient at the height of her symptoms. It was green, ropy and slightly alkaline. It gave positive amylase and trypsin reactions. Lipase was not tested for. The Gmelin test was positive. The Pettenkoffer test for bile salts was positive. Urobilinogen was present in a dilution strength of 600 and urobilin in a dilution strength of 1,600. The urine contained no urobilin or urobilinogen. Dialysates of the blood plasma gave a negative reaction for bile salts. The agglutination test with the Shiga and Flexner types of dysentery bacillus was negative.

Comment.—Attention is called to the presence of urobilinogen in the duodenal juice. In the absence of increased blood destruction, this is proof of diffuse disease of the liver. This appears to be an instance of celiac disease developing after an acute parenteral infection.

CASE 3.—*History.*—A. O., girl, admitted September, 1921, aged 29 months, weight 20 pounds, height 29½ inches, was breast fed eight months. She was well until she had pertussis at 18 months. Then she began to have frequent vomiting attacks and soon after a diarrhea developed. At the time of the onset of this trouble the diet consisted largely of milk, eggs, potato, bread and butter. Vomiting continued practically up to the time of entrance to hospital (i. e., eleven months); diarrhea was present most of the time.

Examination.—The spleen was palpable but not so the liver. The stools were large, gray, fatty and foul. Oct. 24, 1921, there was no free hydrochloric acid and only a trace of total acid. Feb. 9, 1922, the free hydrochloric acid was 9, and the total acid 27.

Treatment.—This child showed great improvement on skimmed lactic acid milk and curd. As she improved, the liver edge came down below the costal margin. Her present height is 33 inches, weight 27 pounds.

April, 1922: Total fat intake in five days, 185 gm.; total weight of dried stool for five days, 65.6 gm.; total fat lost, 21.8 gm.; per cent. lost as neutral fat, 11; per cent. of fat utilized, 89.

Duodenal juice was green, ropy, slightly acid, but contained no urobilinogen. It contained urobilin in a strength of 1,000 dilutions. It gave positive amylase and trypsin reactions. The juice was rendered alkaline before ferment tests were made. It gave a positive Pettinkoffer test for bile salts.

Comment.—This is an instance of celiac disease developing after an attack of pertussis. Tests for liver function were not made during the height of the symptoms.

CASE 4.—*History.*—F. D., girl, born in 1913, was nursed until 15 months of age. When 1 year old, Horlick's malted milk was added to the breast milk. She was weaned from the breast at 15 months; then fed mainly on bread and butter and Horlick's malted milk. She did not like cow's milk. She failed to gain. The stools were foul and gray. In 1917 she stopped walking. In 1918 her height was 34 inches, weight 24 pounds. She had a severe secondary anemia; the spleen was moderately enlarged.

Treatment.—Two transfusions were given. The digestive condition gradually improved, with occasional remissions. When she was 6 years old her weight was 28 pounds; height, 36 inches. The spleen was 3 cm. below the costal margin. The liver was palpable.

Blood: The hemoglobin was 50 per cent.; red blood cells, 4,400,000; white blood cells, 5,600. Differential count: polymorphonuclears, 45 per cent.; small lymphocytes, 49 per cent.; large lymphocytes, 1 per cent.; transitionals, 5 per cent.

When she was 7 years old her weight was 31 pounds; height, 40 inches. The spleen was 3 cm. below the costal margin. The liver was palpable 2 cm. below the costal margin.

In 1921, at 8 years, she weighed 35 pounds. Her height was 40 inches. The spleen was 4 cm. below the costal margin. The urine contained no urobilin or urobilinogen. Gastric contents were totally anacid.

Blood: Hemoglobin, 70 per cent.; red blood cells, 4,400,000; white blood cells, 2,800; polymorphonuclears, 78 per cent.; lymphocytes, 22 per cent.

In January, 1922, profuse hemorrhage from the bowel was followed by a return of the indigestion. She was now 9 years old; weighed 36 pounds, and measured 42 inches in height. The spleen was 7 cm. below the costal margin. The liver was 1 cm. below the costal margin. Bile pigments were in the stool; of bilirubin there was a trace; urobilin and urobilinogen were present.

Blood: Hemoglobin, 40 per cent.; red blood cells, 2,900,000; white blood cells, 2,000; polymorphonuclears, 68 per cent.; small lymphocytes, 28 per cent.; large lymphocytes, 2 per cent., and eosinophils, 3 per cent.

There was a progressive diminution of leukocytes. The blood platelets numbered 440,000. The clotting time was seven minutes; the bleeding time, five minutes.

The total fat intake in five days was 120.45 gm.; the total weight of wet stools for five days was 234 gm.; the total weight of dried stools for five days was 52.2 gm.; the total fat lost in five days was 23.6 gm. Before splenectomy the neutral fat was 8.5 gm.; fatty acid and soaps, 15.1 gm.; per cent. of excreted fat split, 64; fat utilized, 72 per cent. of fat intake.

March 3, 1922, a large fibrous spleen, resembling the spleen of Banti's disease, was removed. The total fat intake in three days was 72.25 gm.; the total weight of dried stools for three days was 24.7 gm.; the total fat lost in three days was 7.41 gm. Three weeks after splenectomy, the neutral fat was 2.52 gm.; fatty acid and soaps, 4.89 gm.; per cent. of excreted fat split, 64; fat utilized, 90 per cent.

Gastric contents: Free hydrochloric acid, 18; total acid, 60.

Comment.—This is an instance of celiac disease developing in a child on a malted milk and bread and butter diet. Later an affection resembling Banti's disease was made manifest.

Attention is called to the usual association between splenic disease of this character and liver disease, and, furthermore, to the probable infectious causation of Banti's disease.

Case 5.—*History.*—M. E., girl, aged 3 years, entered in March, 1921, complaining of celiac disease. Her history states that she was fat and healthy when weaned at 7 months. She then went on a diet consisting mainly of cow's milk and potato. When 18 months of age she had pertussis; but her mother states that before this time her abdomen was distended and that she was passing voluminous foul stools.

Examination.—She was unable to walk; her abdomen was distended, her height was 32 inches and her weight 19 pounds. The stools were large, gray, foul and fatty. Urobilin was present. Repeated gastric analyses showed an absence of free hydrochloric acid. The liver when first examined was no wider than two ribs and an interspace. After one week's treatment the liver edge was palpable 2 cm. below the costal margin.

This child's present weight is 26 pounds and her height 34 inches. The gain of 2 inches in height has been made in the last two months. She is still on lactic acid milk and still has an achlorhydria. She is now running about and plays normally.

Comment.—This is a case of celiac disease apparently resulting from improper feeding, although pertussis may have played some part in its causation.

Attention is called to the extremely small size of the liver when the patient was first examined.

Case 6.—*History.*—E. A., boy, born July, 1916, was breast fed for nine months. Then he was weaned, and thereafter for more than two years his diet consisted mainly of potato and cow's milk. During his second year he had frequent attacks of diarrhea and his abdomen became very much distended. During his third year, the indigestion gradually increased, and on two occasions he had general convulsions.

He came under my care at the age of 3¼ years. His weight was 23 pounds, height 32 inches. The abdomen was distended. Musculature was fairly good. The stool was voluminous, gray, foul, fatty and contained urobilin.

During the next eighteen months this child increased 7 pounds in weight and had become able to handle a fairly general diet. His abdomen was still distended and his stools still rather light colored and voluminous, but were not foul or noticeably fatty.

Comment.—This is an instance of celiac disease developing while the patient was being fed nearly altogether on milk and potatoes.

Case 7.—*History.*—E. B., girl, was admitted June 7, 1921, aged 14 months; weight, 17 pounds. She had been breast fed seven weeks; thereafter was fed on cow's milk mixture. She had a diarrhea since she was 3 months old. At first the stools were greenish in color, but gradually they became whiter. In spite of her digestive disturbance, her general condition improved steadily, and when 11 months of age she was plump and beginning to walk. At this time she had chickenpox, and thereafter she stopped walking and became weaker and thinner.

Examination.—Her abdomen was distended; she had a secondary anemia; her spleen was palpable, and her stools were large, white and foul. She was transfused twice.

Treatment.—This child showed great improvement on skimmed lactic acid milk and curd. The gastric juice has been examined repeatedly and shows no free hydrochloric acid. She is now 32 inches tall, weighs 30 pounds and is beginning to walk. Her duodenal juice is green, ropy and slightly alkaline. It contains no urobilinogen. It contains urobilin in a strength of 600 dilutions. It gives positive tests to bilirubin, to bile salts, to trypsin and to amylase.

April 1, 1922: The total fat intake for five days was 185 gm.; the total weight of the dried stool for five days was 111 gm.; the total fat lost for five days was 37.7 gm.; per cent. of neutral fat, 12; per cent. of fat utilized, 81.

Comment.—This is an instance of celiac disease developing in an artificially fed young infant, the symptoms of which were exaggerated by an intercurrent parenteral infection.

Tests of liver function were not made at the height of disease.

THE TREATMENT OF FLAT WARTS BY THE INTERNAL ADMINISTRATION OF MERCURY *

HOWARD FOX, M.D.
NEW YORK

The suggestion of treating flat warts by the internal administration of mercury was first made by Dr. Charles J. White[1] in 1915. This method of treatment was tried on the supposition that warts were caused by some as yet undiscovered protozoon. In his first paper White reported seven cases and four additional cases were reported in a subsequent communication. All of the eleven cases, except one, showed a most favorable response at the end of a few weeks to the internal use of some form of mercury. Four of White's patients were adults, the ages of the others varying from 7 to 14 years. In addition to the internal medication, some of the patients were also treated locally by salicylic acid or other remedy.

The disease in question is often spoken of as verruca plana juvenilis, though it is by no means confined to juvenile patients. It generally appears on the face and hands, and in men is apt to affect the bearded region. The eruption consists of flat, pinhead sized, or larger, flesh colored, or slightly pinkish yellow, more or less polygonal papules. They may be discrete or aggregated (Fig. 1).

My personal experience in trying the method suggested by White is confined to eleven cases, one of which is not suitable for analysis as the patient was treated by another physician with the roentgen ray after she had taken mercury for one week. The result in this case was successful at the end of a few weeks. Of the ten cases in which the mercury treatment was given a fair trial the result was entirely successful in five. In these cases the disappearance of the eruption was absolutely complete in from three to eight weeks. There had, furthermore, been no return of the disease in these patients at the end of one, three, four and seven months and three years, respectively. The treatment consisted solely of the internal administration of mercurous iodid tablets in doses of ¼ grain, three times a day. Smaller doses were given the younger patients. No local remedies whatever were employed. In the five unsuccessful cases there was no improvement after two or four weeks of treatment.

---

* Received for publication, Oct. 25, 1922.

[1] White, C. J.: The Use of Mercury in Verrucae Planae Juveniles, J. Cutan. Dis. **33**:731 (Nov.) 1915; **34**:361 (May) 1916.

One of the most striking results was noted in the case of a young lady of 24 who had suffered for eight months from a profuse eruption of flat warts of the face and left hand. At the end of three weeks every lesion had completely disappeared without leaving a trace. Another patient who responded to treatment in a most satisfactory manner was a boy, aged 10 (Fig. 1), who had suffered for two months from an eruption of the face, forearms and left hand. He was given mercurous iodid tablets in doses of ¼ grain, three times a day. At the end of seventeen days the eruption had entirely disappeared from the face leaving a few ill defined pigmented spots in place of the former lesions. On the hand the eruption had not quite disappeared. Mercury was continued for another week and was followed by the disappearance of the eruption on the hand. This patient was presented before the New York Dermatological Society on May 16, 1922.[2] In the discussion that followed Dr. Paul Bechet remarked that "the value of the mercurous iodid in the treatment of this condition had been demonstrated in a number of cases." He recalled a patient who recovered after a few

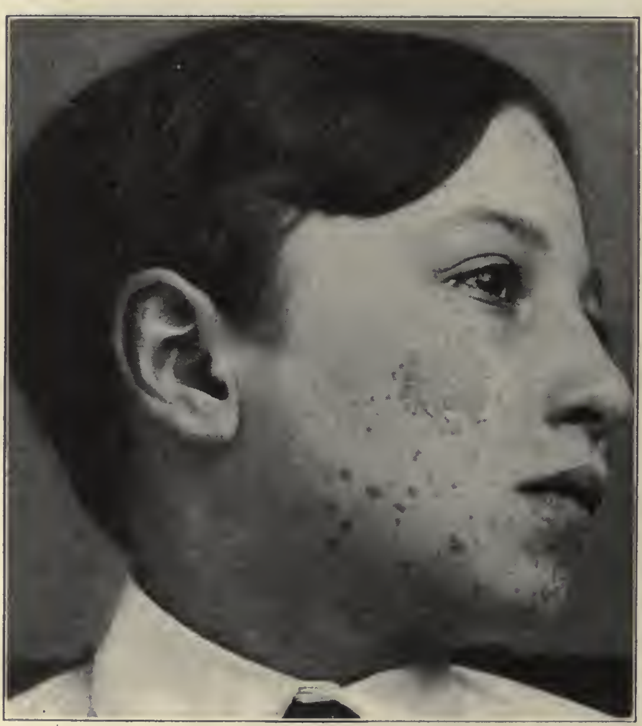


Fig. 1.—Flat warts (verrucae planae juveniles) of two months' duration in a boy, aged 10 years.

---

[2] Arch. Dermat. & Syph. **6**:384 (Sept.) 1922.

weeks of treatment. Dr. Charles M. Williams stated that he had treated a number of cases by Dr. White's method and that "the first four patients made remarkable recoveries in from ten days to four weeks but the next patients did not improve at all." He added that "there was a class of warts for which mercurous iodid seemed to be effective, but it was impossible to tell beforehand what the result would be." Dr. H. H. Whitehouse remarked that "mercurous iodid was not effective in all cases and often failed." He had under observation a case "which improved to a certain degree but then stopped and new lesions were constantly appearing." Dr. Hans Schwartz reported two cases "which had cleared up entirely under treatment with mercurous iodid" and Dr. J. M. Winfield said that he had "treated a number of patients with mercurous iodid. It seemed to be a wonderful remedy in certain cases."

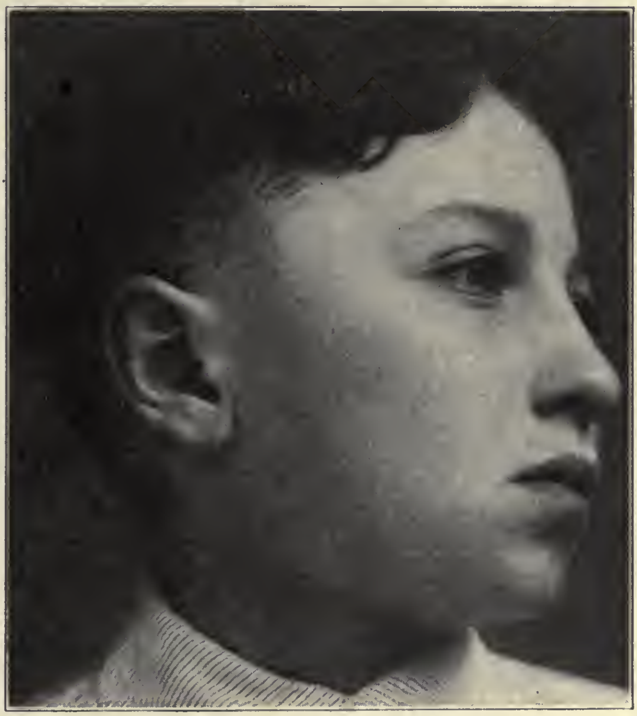


Fig. 2.—Seventeen days after ingestion of mercurous iodid, ¼ grain, three times a day.

From my own limited experience and the remarks quoted there seems to be no doubt that in a certain proportion of cases of flat warts, successful results can be obtained by such a simple procedure as the administration of mercury by mouth for a few weeks. This method of treatment is comparable to the effects of radiation on common warts (verruca vulgaris). At times the results of radium or roentgen-ray treatment are brilliant, at other times they are entirely unsuccessful. Flat warts can always be removed by the curet, a method, however, which is not an agreeable one, especially for the average child or young woman. It is also well known that various types of warts may suddenly disappear spontaneously. As the mercury treatment is such a simple one, even though it often fails, it would seem rational to give it a trial before resorting to other less agreeable methods.

Cases of Flat Warts Treated by Internal Administration of Mercury

No.	Name	Sex	Age	Duration of Disease	Location of Disease	Duration of Treatment	Result
1	J. C.	F.	18	1 year	Face	1 month	Successful; no return at end of 1 month
2	M. B.	F.	24	8 months	Face and hands	3 weeks	Successful; no return at end of 3 years
3	D. N.	M.	46	Not recorded	Hands	3 weeks	Failure
4	N. W.	M.	36	18 months	Beard	3 weeks	Failure
5	D. A.	F.	16	3 years	Face and hands	3 weeks	Failure
6	I. S.	F.	27	4 years	Face and fingers	2 weeks	Failure; spontaneous disappearance 6 months later
7	F. G.	F.	23	1 year	Hand	4 weeks	Failure
8	S. W.	M.	10	2 months	Face, hands and forearms	4 weeks	Successful; no return at end of 7 months
9	E. G.	F.	3½	1 year	Face	3 weeks	Successful; no return at end of 4 months
10	B. K.	F.	5	1 year	Face	4 weeks	Successful; no return at end of 3 months

COMPARISON OF DIPHTHERIA IMMUNITY IN THE MOTHER AND IN THE NEW-BORN *

H. O. RUH, M.D., AND J. E. McCLELLAND, M.D.
CLEVELAND

The question of transference of antibodies, protein sensitization and infection, from mother to child has been studied much. Numerous investigators at various times have worked intensively on this subject.

The most easily proved transference of immune bodies occurs in the case of the well known immunity to diphtheria, which is present in a high percentage of new-born infants. This may be investigated either by examination of the cord blood serum, or by the intradermal toxin test (Schick test).

The most intensive studies on the diphtheria antitoxin content in mother and new-born that we have been able to find were made by von Groer and Kassowitz.[1] They made quantitative estimation on the antitoxin content of umbilical cord blood serum in 143 new-born infants, and compared these results with like estimation made on the blood serum of the mothers. They also did intradermal toxin injections in all of these patients, and also intradermal toxin-antitoxin injections in the mothers, first making comparison between antitoxin content of sera in mothers and new-born, and second between the cutaneous reactions. Of 143 mothers, twenty-three, or 16 per cent., showed no immune bodies in the serum, while 120, or 84 per cent., showed immune bodies present. Corresponding results were found in the offspring. The intradermal tests did not give similar results; ninety-one, or 63.6 per cent., of the mothers reacted positively, while only seven, or 4.9 per cent., of the babies gave positive reactions. In view of later work we do not feel that the markedly high percentage in the mother, and the small percentage in the babies can be accepted as it is now generally believed that from 15 to 20 per cent. of adults and infants give positive intradermal reactions; the most plausible explanation is that they were using too strong a toxin, although this leaves us at a loss to explain why so few positive reactions were obtained on the babies unless it was due to the technical difficulties of the intradermal injection in the new-born, which we shall mention later.

---

* Received for publication Oct. 23, 1922.

* From the Nurseries of Maternity Hospital and the New-Born Clinic, St. Luke's Hospital.

[1] von Groer and Kassowitz: Ueber das normale Diphtherie-antitoxin bei Mutter und Neugeboren, Ztschr. f. Immunitätsforsch. u. Exper. Therap. **23**:108 (May) 1914.

In 1917 Zingher [2] reported comparative results with the Schick test in mothers and infants up to the age of 24 months. The ages of the infants are not given exactly, but in three months groups. The series of infants up to the age of 3 months (twenty-three) is too small from which to draw conclusions. In eighteen instances, both mother and infant reacted negatively; in four instances both mother and infant reacted positively; in one case the mother gave a negative reaction, while the infant was positive, and in no instance did the mother react positively and the infant negatively.

In order to make further observations on the incidence of transference of diphtheria antitoxin from mother to child, we decided to make tests in 100 mothers and their new-born babies.

METHOD

Kind of Toxin.—The bulk toxin manufactured by the New York City Board of Health was used in all the tests. Fresh dilutions were made for each day's tests. In half the cases one-fortieth the minimum lethal dose was given in 0.2 c.c. and in the other half one-fiftieth the minimum lethal dose was given in 0.1 c.c. sterile saline. Intradermal injection was found much more difficult in the infants than in the mothers. Different sites on the arms and legs were tried without finding one more advantageous than another. The difficulty seemed to be due to the peculiar character of the infant skin. It was found that greater pressure is required to deliver the solution intradermally in an infant than in an adult. With the same technic the wheal is found to be considerably smaller in the infant and disappears much more quickly. Time determinations were made in ten infants and ten mothers; the averge time for disappearance of the wheal in the babies was three and a half minutes, while in the mothers it was twelve minutes. We are making histologic studies to determine, if possible, what factors are responsible for these differences. Some of the reactions mentioned below can probably be explained on the basis of the histologic structure of the skin in the new-born.

All the babies in this series were less than 7 days of age when tested. Most of the reactions were read at the end of two days and four days, and all were read at the end of a week. No control tests were made for pseudoreactions, but the repeated readings disclosed no pseudoreactions occurring in these very young infants. If the reaction was positive in twenty-four hours, it always persisted strongly positive at the final reading. In two babies the cutaneous reaction was slight, but was accompanied by a deep infiltration in the skin and subcutaneous tissue, probably due to the rapid escape of toxin into the deeper tissues. A consistent difference in the intensity of the positive reaction was observed between mother and infant; the mother uniformly giving a more strongly positive reaction than her infant. Vesication was never seen in an infant, although it occurred in several of the mothers.

---

[2] Zingher, A.: Further Studies with the Schick Test, Arch. Int. Med. **20**:392 (Sept.) 1917.

RESULTS

Ninety-five mothers and their babies gave corresponding reactions; twenty were positive and seventy-five were negative.

Four mothers gave positive reactions and their babies negative reactions; one of these babies was two months premature. If the transference of dihphtheria antibodies always occurs, as we believe, these negative reactions could best be explained, on imperfect technic, in the infants on account of the peculiarities of the skin, alluded to above. Negative reactions in the premature might be explained by the inability of the underdeveloped tissues to react to the toxin stimulus. We hope later to be able to publish a curve showing the relationship between the antitoxin content of serum and the fetal age.

TABLE 1.—Intradermal Diphtheria Toxin Reactions in One Hundred Mothers and New-Borns

Mother and Baby Positive	Mother and Baby Negative	Mother Positive Baby Negative	Mother Negative Baby Positive
20	75	4	1

TABLE 2.—Comparative Results of Intradermal Diphtheria Toxin Reactions in Mothers and New-Borns

	Negative, Per Cent.	Positive, Per Cent.
Mothers	76	24
New-Born	79	21

In only a single instance was a positive reaction found in the baby with a negative reaction in its mother. This result we are not able to explain, unless the baby had absorbed from the mother more immune bodies than the mother had retained (Tables 1 and 2).

The close agreement in reaction between mother and baby seems to imply a direct transference of antitoxin immunity from mother to child. Eight of the babies giving negative reactions did not receive breast milk or colostrum before the reactions were read. It is evident, therefore, that they received their immunity from the mother before birth. We concur with von Groer and Kassowitz that by the frequency of this phenomenon it must be considered a normal function of the placenta to transmit the antitoxin bodies from mother to child.

CHEMICAL STUDIES OF THE BLOOD OF MOTHER AND FETUS *

MARION G. HOWE AND MAURICE H. GIVENS
PITTSBURGH

The nutrition of the human fetus is a difficult subject to study on account of the almost complete isolation of this body. The physiologic activities of mother and offspring, as well as the rôle the placenta has played in the development of the latter, must be represented to a certain degree by the products of metabolism circulating in the blood streams of both organisms. By comparison of the amounts of nutriments and waste substances simultaneously present in the blood of each of the two subjects some information ought to be obtained concerning the "parasitic existence" of the fetus. Slemons [1] in particular has contributed some data to the question. However, the need for more positive evidence has led us to extend this type of work.

Do the derivatives of the protein and fat in the maternal intake reach the fetus in the form of "building stones" (such as amino-acids, etc.) or resynthesized products? Colloids have been shown not to traverse the placenta. Ascoli,[2] introducing egg albumin into pregnant animals subcutaneously or by the digestive tract, could detect it by the precipitin test in the material blood but not in the fetal blood. Mendel and Daniels [3] injected Sudan III into the circulation of pregnant rats; although the dye stained the maternal fat readily, it could not be found in the placenta or in the fetal body. More recently, Slemons and Stander,[4] studying the fat content of human maternal and fetal blood, found such a difference between the two that their results in conjunction with those of Mendel and Daniels led them to believe "that fat is not included among the materials contributed by the parent to her offspring.[5]" They likewise consistently found cholesterol and lecithin in greater amounts in the maternal blood than in the fetal blood. This observation is not in accord with a former study of Slemons and

---

* Received for publication, Oct. 23, 1922.

* From the Research Laboratories, Western Pennsylvania Hospital.

* The data in this paper are taken from an essay presented by Marion G. Howe to the Faculty of the Graduate School, Yale University, 1921, in partial fulfilment of the requirements for the degree of Master of Science.

[1] Slemons, J. M.: The Nutrition of the Fetus, Yale University Press, 1919.

[2] Ascoli, A.: Ztschr. f. Physiol. Chem. **36**:498, 1902.

[3] Mendel, L. B., and Daniels, A. L.: J. Biol. Chem. **13**:71, 1912

[4] Slemons, J. M., and Stander, H. J.: Cited by Slemons.[1]

[5] Quoted from Slemons,[1] p. 39.

Curtis [6] in which they report identical quantities of cholesterol in the blood of mother and fetus.

Several investigators have indicated that there is a free exchange of crystalloids between mother and offspring. Sugar has been found by Morriss [7] to be present in greater quantity in the maternal than in the fetal blood but not in such quantities as to be unexplained by diffusion. Morse [8] reported a greater amount of amino-acids in the fetal blood. Although the difference is small, it is so constantly present that he concludes that the passage of amino-acids from mother to fetus cannot be explained by diffusion entirely. Stander and Tyler [9] reported what appear to them equal concentrations of ash in maternal and fetal plasma. There is likewise apparently free passage of waste products through the placenta. Slemons and Morriss [10] found such values of urea in both bloods that they considered them identical. Slemons and Bogart,[11] also Kingsbury and Sedgwick,[12] reported similar findings for uric acid; Plass,[13] and Hunter and Campbell [14] for the creatinin and creatin of the plasma.

As a result of the investigations, briefly reviewed, Slemons has concluded that the placenta acts like a semipermeable membrane through which the soluble substances pass by simple diffusion.

Experiments demonstrating the enzymatic action of placental tissue have led some to believe that this organ is actively engaged in preparing food in the proper form for the developing fetus; also, that it is endowed with power to yield excretory products. Hofbauer [15] demonstrated that glycerin extracts of the placenta contained glycolytic ferments; Hammett [16] showed that the quantity of urea increased in an aqueous suspension of placental tissue in the presence of a preservative; Cannata [17] noted that the placenta will break down uric acid. Contrary to the above results Morriss [7] has shown that the blood of twins, each with its own placenta, contained almost identical quantities of sugar (0.003 gm. difference per hundred cubic centimeters blood) and exactly identical quantities of nonprotein nitrogen. If the presence of either of these substances, the nonprotein nitrogen representing several nitrogenous constituents, depended on the enzymatic action of the placentas in this case of twins, one would hardly expect such precise quantitative correspondence.

---

[6] Slemons, J. M., and Curtis: Am. J. Obst. **75**:569, 1917.

[7] Morriss, W. H.: Bull. Johns Hopkins Hosp. **28**:140, 1917.

[8] Morse, A.: Bull. Johns Hopkins Hosp. **28**:199, 1917.

[9] Stander, H. J., and Tyler, M.: Surg., Gynec. & Obst. **31**:276, 1920.

[10] Slemons, J. M., and Morriss, W. H.: Bull. Johns Hopkins Hosp. **27**: 343, 1916.

[11] Slemons, J. M., and Bogart, L. J.: J. Biol. Chem. **32**:63, 1917.

[12] Kingsbury, F. B., and Sedgwick, J. P.: J. Biol. Chem. **31**:261, 1917.

[13] Plass, E. D.: Bull. Johns Hopkins Hosp. **28**:137, 297, 1917.

[14] Hunter, A., and Campbell, W. R.: J. Biol. Chem. **34**:5, 1918.

[15] Hofbauer: Cited by Morriss.[7]

[16] Hammett, F. S.: J. Biol. Chem. **37**:105, 1919.

[17] Cannata, S.: Fol. clin., **2**:34, 1911.

EXPERIMENTAL

The subjects for study were patients at full term in the department of obstetrics of the Western Pennsylvania Hospital, Pittsburgh. In virtually all of the cases an anesthetic was administered—generally nitrous oxid and oxygen analgesia during part of the first and all of the second stage, the labor being ended under complete anesthesia by combining ether with the nitrous oxid. In a few of the cases the sole anesthetic was ether given only at the end of the second stage. A few of the patients were delivered by forceps, under ether anesthesia.

The blood of the fetus, taken from the placental end of the cord as soon as it was cut, was allowed to flow into a small sterile bottle containing sufficient potassium oxalate (usually 25 mg.) to prevent clotting. Coincidently, as nearly as possible, blood was taken from a vein in the mother's arm.

The methods of analysis were those of Folin and Wu[18] on tungstic acid filtrates involving the improved procedure[19] for sugar determination.

Although creatinin determinations were made on twelve sets of maternal and fetal bloods, the colorimetric readings were so unsatisfactory that the results have not been tabulated despite the fact that the averaged data agreed closely.

Virtually equal concentrations of creatinin have been found in maternal and fetal plasmas by other investigators. Hunter and Campbell[20] report that in whole blood some substance is freed, by the Folin technic, from the corpuscles which contributes to the color and is variable. Plass,[13] independently, came to the same conclusions. By two different methods he could find no regular relationship between the whole bloods but values for the plasmas agreed closely.

The results for nonprotein and urea nitrogen are recorded in Table 1. The nonprotein nitrogen content of the mother's blood is not the same as that of her offspring in every case; a similar discrepancy appears in the case of urea. However, if the average value for each of these constituents in maternal and fetal blood is calculated, one is confronted with almost identical figures. The average nonprotein nitrogen for mothers' blood is 23.8 per hundred cubic centimeters; for fetal blood it is 23.8 per hundred cubic centimeters of blood; the average urea nitrogen for mothers' blood is 11.8 per hundred cubic centimeters; for fetal blood it is 10.9 per hundred cubic centimeters blood. Despite the identity of these averages, marked differences in individual cases may still exist and be of significance. The differences given by Slemons[1] are also tabulated in Table 2. He does not consider the variations significant but concludes that the concentration of nonprotein nitrogen and urea is equal in maternal and fetal bloods. We hesitate to disregard entirely these differences in the case of urea especially. All the bloods were obtained within a few seconds to a very few minutes of each other, and where the greatest variation occurred, 4.2 mg., the time of collection of the two bloods was identical.

---

[18] Folin, O., and Wu, O.: J. Biol. Chem. **38**:81, 1919.

[19] Folin, O., and Wu, O.: J. Biol. Chem. **41**:367, 1920.

[20] Hunter, A., and Campbell, W. R.: J. Biol. Chem. **32**:195, 1917.

TABLE 1.—Nonprotein Nitrogen and Urea Nitrogen; Mg. Per 100 C.c. of Blood

No.[*]	Para	Source	N. P. N.	Difference in Favor of		Urea N.	Difference in Favor of		Remarks
				M[†]	F[†]		M	F	
5	I	M	....	...	...	13.2	1.5	...	Nitrous oxid, whiffs of ether
		F	....	...	...	11.7			
6	I	M	28.0	...	1.1	17.2	1.4	...	1′ 48″ nitrous oxid
		F	29.1	...	...	15.8			
9	I	M	24.6	0.5	...	13.6	2.6	...	Ether
		F	24.1	...	...	11.0			
11	I	M	23.8	0	0	11.4	1.8	...	2′ nitrous oxid,
		F	23.8	...	...	9.6			
14	I	M	21.3	0	0	10.5	...	0.1	1′ 57″ nitrous oxid
		F	21.3	...	...	10.6			
16	I	M	22.2	4.2	...	10.8	0.6	...	15″ ether; syphilis
		F	18.0	...	...	10.2			
3	II	M	....	...	...	9.7	1.1	...	No anesthesia
		F	....	...	...	8.6			
4	II	M	....	...	...	9.7	0.4	...	No anesthesia
		F	....	...	...	9.3			
7	II	M	27.6	...	2.1	13.1	0.1	...	2′ 18″ nitrous oxid
		F	29.7	...	...	13.0			
10	II	M	26.1	0.6	...	10.9	0.4	...	Nitrous oxid, ethylchlorid and ether
		F	25.5	...	...	10.5			
15	II	M	21.7	...	2.6	13.9	1.9	...	30″ nitrous oxid
		F	24.3	...	...	12.0			
13	III	M	21.5	...	0.6	11.0	0.9	...	Whiffs of ether
		F	22.1	...	...	10.1			
8	IV	M	22.1	1.8	...	9.5	0.2	...	Nitrous oxid
		F	20.3	...	...	9.3			
17	IV	M	....	...	...	11.7	0	0	Whiffs of ether
		F	....	...	...	11.7			

[*] The case numbers in Tables 1, 4 and 6 are the same. There was a small clot in the fetal blood in Cases 2, 4, 5, 10, 12 and 16. The clots were too small to make an appreciable difference. Furthermore, the distribution of the constituents in plasma and corpuscles is such that a clot would not alter analytical results.

[†] M denotes mother; F, fetus.

Table 2 has been constructed on the assumption that 0.5 mg. or more is an actual difference, that is, beyond the range of technical variation. The nonprotein nitrogen represents urea, amino-acids, creatinin, uric acid and rest nitrogen. Why does not the greater amount of amino-acids in the fetal blood, evidence for which has been given previously, cause a corresponding difference in the nonprotein nitrogen? In 57 per cent. of our cases the urea was higher in the maternal blood, the average increase being 1.5 mg. per hundred cubic centimeters of blood. The concentrations of creatinin are practically equal. In the case of uric acid, it will be noted presently that there is apparently a slight retention in the fetus. May not the greater quantity of urea nitrogen in the mother's blood counterbalance the excess of amino-acid nitrogen in the fetal blood? If such is the case, it helps to explain why there is not a regular preponderance of nonprotein nitrogen in favor of the fetus.

TABLE 2.—SLEMONS' DIFFERENCES

Mg. N. P. N. in Favor of		Mg. Urea N in Favor of	
Mother	Fetus	Mother	Fetus
...	0.3	0.4	...
...	0.7	...	0.9
1.7	...	0.9	...
1.0	...	...	1.9
0.5	...	0	0
3.5	...	1.4	...
0	0	0.9	...
...	1.3	...	1.4
1.7	...	1.4	...
0.3	...	0.5	...
0	0	...	0.9
...	1.0	...	0.9
...	0.5	...	0.4
5.5	...	0.5	...
3.0	...	1.4	...
...	0.2	0.9	...

Whether this difference in urea content is of any significance and of what it is significant we are not prepared to say. The well known fact that animal tissues, in general, are very permeable to urea makes one pause to consider any difference in concentration of this substance in two solutions separated by a membrane. The average difference—1.5 mg. of urea nitrogen—is equivalent to 3.2 mg. of urea. Therefore, in 57 per cent. of the cases studied the mother has 3.2 mg. more of urea in each 100 c.c. of whole blood than the fetus. One possible explanation in this connection is that the maternal kidneys do not remove the urea quite as rapidly as it is brought to them. The fetus is in need of a great deal of nitrogenous material, especially near the end of gestation, and the waste therefrom must be removed. Another suggested explanation is that the membrane may be impaired by various factors incident to delivery so that at parturition equal concentrations cannot be maintained. It is also conceivable that the number of cells undergoing metabolism is much greater in the mother than in the fetus. Neither anesthesia nor surgical intervention affect apparently either the nonprotein nitrogen or the urea. Of course, a final answer to this phase of the subject cannot be given until analyses of blood are secured in cases involving the two possible interfering factors. Finally, instead of being due to a temporary derangement of the membrane, the difference may be due to individual imperfections that have kept such a variation between maternal and fetal blood quite constant throughout pregnancy. In considering the 57 per cent. of cases in which there was an excess of urea in the maternal blood, it must not be forgotten that 43 per cent. of the cases were identical. The small variation has been discussed at some length because not only does it seem especially significant in the case of urea, but it raises the question whether a slight quantitative difference in other constituents of the blood of mother and fetus is really significant.

TABLE 3.—COMPARATIVE TABLE CONSTRUCTED FROM TABLES 1 AND 2

	Number of Cases	Identical, per Cent.	In Favor of		Average Difference	
			Mother, per Cent.	Fetus, per Cent.	Mother, Mg.	Fetus, Mg.
N. P. N.						
Authors	10	20	40	40	1.8	1.6
Slemons	16	31	44	25	2.5	0.9
Urea N:						
Authors	14	43	57	..	1.5	...
Slemons	16	19	50	31	0.98	1.20

Does uric acid "enter the maternal circulation as freely as if the placenta did not exist?" From data summarized in the last two columns of Table 5 Slemons,[1] and Kingsbury and Sedgwick [12] have answered this question in the affirmative. Slemons' values are from normal patients. Kingsbury and Sedgwick make no statement in regard to this point, but presumably, judging from their values, the data are normal.

The third column summarizes results of Slemons' studies in which there are involved such complications as nephritis, preeclamptic toxemia, induction, deep chloroform, and premature twins. The complications are of such different type that it is doubtful whether anything is gained by grouping them. At least there is little cause to believe that the relationships as brought out by the table are altered in any characteristic way by such heterogenous factors. The resemblance to our results is striking. They can be interpreted in no other way than that there tends to be some retention of uric acid in the fetus. The conditions of birth may account for the large excess in Case 15. Delivery was delayed on account of uterine inertia. The fetal heart sounds, taken often, were slow, and the fetus, when delivered, was blue. Before definite conslusions can be drawn in regard to a tendency for a greater amount of uric acid in the fetal blood than in the maternal a careful study of more cases is essential.

TABLE 4.—Uric Acid; Milligrams Per Hundred Cubic Centimeters of Blood

No.	Para	Source	Uric Acid	Difference in Favor of		Interference	Anesthetic Used *	Duration of Labor, Hours
				M	F			
5	I	M F	4.3 5.1	...	0.8	....	Nitrous oxid, whiffs of ether	19
6	I	M F	4.7 5.0	...	0.3	Low forceps	1′ 48″ nitrous oxid	14½
9	I	M F	4.0 3.7	0.3	...	Mid forceps	Ether	29½
11	I	M F	6.9 6.9	0	0	Mid forceps	2′ nitrous oxid; ether	9
14	I	M F	4.2 4.2	0	0	....	1′ 47″ nitrous oxid	14½
16	II	M F	3.5 4.5	...	1.0	Low forceps	15″ ether (syphilis)	9¾
3	II	M F	1.0 0.9	0.1	...	....	....	14
7	II	M F	5.1 5.3	...	0.2	Mid forceps	2′ 18″ nitrous oxid	14
12	II	M F	4.9 4.9	0	0	....	50″ nitrous oxid, whiffs of ether	12
15	II	M F	3.8 5.2	...	1.4	....	30″ nitrous oxid	7
13	III	M F	4.4 3.8	0.6	...	....	Whiffs of ether	38
8	IV	M F	2.9 3.7	...	0.8	....	Nitrous oxid	5½
17	IV	M F	3.2 3.4	...	0.2	....	Whiffs of ether	18

* In the instances where nitrous oxid was used during labor, its administration was for analgesia not anesthesia.

It would seem that either the placenta is a barrier to uric acid or diffusion lags behind accumulation. Almost immediately after birth the fetus urinates so that the fetal kidneys have begun to function some time before parturition. Before birth, then, the transition period has set in when there are two pairs of kidneys operating on each side of the placenta. That this early renal excretion is not very efficient has been shown by Kingsbury and Sedgwick.[12] They found that the blood of new-borns contain more uric acid the first three or four days of life than either maternal or placental blood. It is not out of place to recall here the oft described occurrence of uric acid infarcts in the kidneys of the new-born coming to necropsy. Viewed in this light it is not strange that uric acid, the first substance to be retained by impaired kidneys,[21] should tend to accumulate on the fetal side.

The actual amount of uric acid present exceeds in the majority of cases the upper normal limit. In order to ascertain whether such high values are characteristic of pregnancy the blood of pregnant patients, otherwise normal, was examined. The results are given in Table 6. The values are quite within the normal range, from 1 to 3.5 mg. uric acid per hundred cubic centimeters blood. Slemons has noticed a similar increase in uric acid in the blood of mother and fetus at parturition and explains it as possibly being due to a temporary renal insufficiency quite characteristic of labor. It has already been noted that uric acid is the first of the waste products to be retained in disorders of the kidney. This fact makes it quite possible to have a retention of uric acid and no retention of urea (Table 1). We are inclined to believe that the uric acid content is higher in primiparas. There is no value in Table 4 below 3.5 mg.; the highest is 6.9 mg. No doubt, a harder labor is associated with a greater renal disturbance. Not only a decreased urinary output but possibly an increased formation accounts for the high uric acid. It will be noticed in Table 4 that several of the higher values accompany prolonged anesthesia. With no anesthesia, the value is only 1 mg. per hundred cubic centimeters of blood. Mann [22] has demonstrated that etherization of dogs causes leukocytosis and it is known that an increase of white cells increases the blood uric acid. This experiment is cited as possibly throwing some light on the relationship between the anesthesia and the amount of uric acid.

TABLE 5.—Comparative Table Constructed from Table 4 and Data of Slemons and of Kingsbury and Sedgwick

	Number of Cases	Identical, per Cent.	In Favor of		Average Difference	
			Mother, per Cent.	Fetus, per Cent.	Mother, Mg.	Fetus, Mg.
Authors	13	23	23	54	0.33	0.67
Slemons, complications involved	15	7	33	60	0.7	0.95
Slemons	12	17	41.5	41.5	0.64	0.3
Kingsbury and Sedgwick	14	7	43	50	0.37	0.27

The results for sugar are recorded in Table 7. The average value for mothers' blood was 0.125 per cent.; for fetal blood it was 0.103 per cent.; the difference being 0.022 per cent. These results agree closely with those of Morriss,[5] making them mutually confirmatory. By the Lewis and Benedict method his mean value for mothers' blood was 0.132 per cent.; for fetal blood 0.115 per cent., and the difference 0.017 per cent.

---

21. Myers, V. G.: Practical Chemical Analysis of Blood, 1921.

22. Mann, F. C.: J. A. M. A. **57**:172, 1916.

That the values recorded for mothers' blood are due to a temporary increase is beyond question. In Table 8 the blood sugar values for women at different periods of pregnancy are given, typical values and all within the range of perfectly normal figures. The average is 0.088 per cent. as against 0.125 per cent., the average of a group of parturient women. The change from a normal blood sugar to what may constitute a condition of hyperglycemia is a rapid one. In Case 5, two hours before delivery the blood sugar was 111 mg. per one hundred cubic centimeters of blood. At delivery it had increased by 48 mg. In Case 3, in which the blood was examined at the very beginning of labor, there was an increase of 31 mg. Our data are substantiated and extended by those of others. Analyses by Schiller[23] show no hyperglycemia during the later months of pregnancy or the first two weeks after. Morriss[7] concludes from his intensive studies that the blood sugar is increased during the second stage of labor, being normal during pregnancy and the puerperium.

TABLE 6.—Uric Acid During Pregnancy; Milligrams Per Hundred Cubic Centimeters Blood

Number	Para	Period, Months	Uric Acid
1	1	2-3	2.5
2	XI	3	3.5
3	V	6	2.7
4	II	6	1.9
5	III	6	3.2
6	IV	8	3.0
7	II	8	3.3
8	I	8½	2.5
9	V	9	1.6
10	II	9	2.8

This relatively high blood sugar content at the end of the second stage of labor is due to one or both of two causes, namely: muscular work and anesthesia including analgesia. In Case 3, one of these factors is ruled out, there being no anesthetic employed. The patient's age (the first pregnancy occurred seventeen years previously) could account for a hard labor. The increase of 31 mg. of sugar per hundred cubic centimeters of blood must be due to the contractions of the uterus and probably to voluntary efforts of the mother. Even during menstrual uterine contractions the blood sugar has been shown to increase slightly.[24] It is not strange, then, that there is a marked increase when this organ is convulsed with the heaviest waves of contraction of which it is capable. In regard to the voluntary muscular efforts of the mother, one cannot claim certainly that they are a contributing factor for it has not been shown that the blood sugar always increased after such muscular

---

23. Schiller, H.: Surg., Gynec. & Obst. **39**:450, 1919.

24. Kahler, H.: Wien. klin. Wchnschr. **27**:417, 1914.

activity. Experimental results are not uniform. Though the response is evidently somewhat variable, there is a rise in most cases.

How much of the high blood sugar is due to an adaptation of the organism to feed the working muscles and how much is due to ether or nitrous oxid it is impossible to say. The effect of the anesthetic alone can never be studied in normal confinements or those approximating normal, because muscular contractions are always present. But several experiments can be cited to show that nitrous oxid, ether and chloroform increase blood sugar. Epstein and Aschnor [25] reporting on fourteen gynecologic operations with nitrous oxid and ether anesthesia showed an increase of 32 per cent. of sugar after the operation. They believe with the exception of nephrectomy that the anesthetic is the important factor and not the operation itself. Obstetric operations were performed in five of the thirteen cases recorded in Table 7, but

TABLE 7.—STUDY OF SUGAR IN BLOOD; GRAMS PER HUNDRED CUBIC CENTIMETERS BLOOD

No.	Para	Age	Source	Sugar	Difference in Favor of M	Interference	Anesthesia	Duration of Labor, Hours
5	I	23	M * M F	0.111 0.159 0.137	0.022	....	Nitrous oxid, whiffs of ether	19
6	I	29	M F	0.160 0.138	0.022	Low forceps	1′ 48″ nitrous oxid	14½
9	I	32	M F	0.127 0.100	0.127	Mid forceps	Ether	29½
11	I	30	M F	0.103 0.092	0.011	Mid forceps	2′ nitrous oxid; ether	9
14	I	22	M F	0.137 0.089	0.048	....	1′ 47″ nitrous oxid	14½
16	I	19	M F	0.088 0.084	0.004	Low forceps	15″ ether	9¾
3	II	37	M † M F	0.122 4.153 0.129	0.024	....	....	14
7	II	24	M F	0.098 0.089	0.009	Mid forceps	2′ 18″ nitrous oxid	14
10	II	28	M F	0.147 0.120	0.027	....	Nitrous oxid, ethylchlorid ether	12
12	II	23	M F	0.112 0.089	0.023	....	50″ nitrous oxid, whiffs of ether	5
15	II	..	M F	0.112 0.097	0.015	....	30″ nitrous oxid	7
13	III	34	M F	0.108 0.082	0.026	....	Whiffs of ether	38
8	IV	39	M F	0.122 0.097	0.025	....	Nitrous oxid	5½

* Two hours before labor. † Before labor.

---

[25] Epstein, A. A., and Aschnor, P. W.: J. Biol. Chem. **25**:151, 1916.

there is nothing distinctive in regard to the maternal blood sugar, except that two of them, Cases 16 and 7, are among the lowest. It is very apparent that the interference cannot account for an increase. Rouzaud [26] reports a hyperglycemia under general chloroform anesthesia and Hirsh [27] the same results with both ether and chloroform. Contrary, then, to the response of the organism to voluntary muscular work, the response to an anesthetic is a regular one, depending on an actual disturbance of the sugar metabolism.

It seems quite probable that a psychic factor may account for some of the increase in blood sugar. Referring again to the work of Epstein and Aschnor [25] no apparent relationship between pain or great fear of the operation and the concentration of sugar could be detected. On the other hand, a neurotic patient of Morriss [7] developed hyperglycemia as the result of a great disturbance over having a sample of blood taken from her arm.

TABLE 8.—Sugar During Pregnancy; Grams Per Hundred Cubic Centimeters Blood

Number	Para	Period, Months	Sugar
1	I	2–3	0.088
2	IV	6	0.082
3	V	6	0.086
4	II	6	0.128
5	IV	8	0.058
6	II	8	0.093
7	I	8	0.085
8	I	8½	0.080
9	I	8½	0.085
10	I	9	0.064
11	II	9	0.125

Age, duration of labor, and number of pregnancies seem to influence the amount of the increase but they are so interwoven that it is difficult to make any definite statements. The average for the six primiparas, even with the comparatively low value in Case 16, is higher than the average of any of the other groups.

Mild hyperglycemia in the mother's blood, brought about by muscular contractions, the anesthetic, and possibly pain and deep emotions has been considered. What of that in the fetal blood? The excess in favor of the mother and the close agreement of the average amount in excess with that found by Morriss has already been noted. This difference is probably due to the fact that sugar is being produced in the mother more rapidly than it can diffuse through the placenta and establish equilibrium. An increase of 32 mg. per hundred cubic centimeters of blood in two hours gives some idea of the rate at which sugar is being poured into the maternal circulation. Where there is

---

26. Rouzaud: Compt. rend. soc. biol. **82**:727, 1919.

27. Hirsh, E.: Z. Physiol. Chem. **93**:355, 1915.

no apparent great increase in the maternal blood, that and the fetal blood are more nearly of equal concentration, as for example, in Cases 11, 16 and 7. Slemons [1] believes the excess sugar in the mother's blood to be an arrangement "on the basis of diffusion" [28] to insure a steady supply for the fetus. An "arrangement" and diffusion are hardly compatible. It would seem that rather than be a special adaptation, the unequal concentrations are the result of physical laws. The sugar in the mother's blood rises very rapidly and diffuses through the placenta but the rate of diffusion cannot keep up with the production.

The distribution between mother and fetus of some of the products that have been considered does not necessitate a complex mechanism to account for the passage of fetal food and waste products through the placenta. They have been found in such amounts as to be most reasonably explained by dialysis which appears to operate in spite of the fact that the pressure in the maternal blood stream is much greater than that in the fetal blood. For this reason, if for no other, the process is hardly a "simple" one. Whether one is justified in interpreting equal concentrations as a result of diffusion, and markedly unequal concentrations as an absence of diffusion, may be disputed. Cholesterol is not normally found in the spinal fluid or only in extremely small concentration, but in certain pathologic conditions it is found in varying amounts, depending on the change that the membranes have undergone.[29] In these cases the meninges becomes partially permeable. A corollary can be drawn in regard to the placenta. There is a possibility of its being partially permeable to some substances. The evidence as far as fats are concerned seems to indicate that no degree of diffusion takes place.[3] Still another possibility is that enzymes can account for both equal and unequal concentrations, but the basis for such an adaptation remains largely speculative. Diffusion affords a more rational explanation.[30]

SUMMARY

Normal values for the content of nonprotein nitrogen and urea nitrogen in maternal blood prevail at parturition.

The concentration of nonprotein nitrogen in maternal and fetal blood is not the same in every case but there is no consistent preponderance in either blood. Inasmuch as the value for nonprotein nitrogen represents the sum of several nitrogenous constituents, it alone cannot be considered as indicating a free interchange of these constituents through the placenta.

---

[28] Quoted from Slemons **1**:36.

[29] Levinson, A.; Landenberger, L. L., and Howell, K. M.: Am. J. M. Sc. **151**:561, 1921.

[30] We are greatly indebted to Dr. Paul Titus for his cooperation in allowing us to take samples of blood from his patients.

In 43 per cent. of the cases studied, the concentration of urea nitrogen in the two bloods was identical. In 57 per cent. of the cases there was an average of 1.5 mg. more urea nitrogen in 100 c.c. of maternal blood than in the same volume of fetal. This excess may be explained by maternal renal insufficiency or impairment of the placenta. It is not obvious whether such a difference is physiologically significant.

The concentration of blood uric acid of parturient women tends to be higher than normal. In 54 per cent. of the cases studied there is an average difference between maternal and fetal blood of 0.67 mg. per hundred cubic centimeters blood in favor of the fetus. The retention may be explained by fetal renal insufficiency.

The concentration of blood sugar is temporarily increased at parturition owing to the anesthetic, muscular contractions and possibly a psychic factor. The maternal values are consistently greater than the fetal. The average difference between the two values in the cases studied is 22 mg. per hundred cubic centimeters blood. We believe this difference is due to the fact that the rate of production is greater than the rate of diffusion.

Diffusion offers the most reasonable explanation for the passage of nutrients and waste products through the placenta.

THE COLLOIDAL GOLD REACTION IN ACUTE POLIOMYELITIS *

JOSEPH C. REGAN, M.D.; ABRAHAM LITVAK, M.D.
AND
CATHERINE REGAN, M.D.
NEW YORK

The reactions obtained with the colloidal gold test in syphilitic diseases of the central nervous system and the various forms of meningitis are fairly well established and have proved of value in diagnosis. Several investigators have reported their results with the reaction in cases of acute epidemic poliomyelitis, most of the studies having been carried out during the 1916 epidemic. These papers have been quoted at length in a previous publication [1] and will not again be referred to here.

One of us (J. C. R.) previously reported [1] a series of twenty-one cases including seventy-four spinal fluids examined at intervals varying from the fourth to the one hundred and twenty-third day of the disease. The results obtained in this previous series and in the present one have been fairly uniform. Any differences will be called attention to in the accompanying text.

From June to November, 1921, forty-nine cases of acute poliomyelitis were received at the Kingston Avenue Hospital. Eight patients died, a mortality of 16.3 per cent. The ages of the patients varied from 1 year or less to 21 years. The types of the disease were: Myelitic, 38.8 per cent.; bulbopontine, 14.3 per cent.; polyneuritic, 2 per cent.; Landry's paralysis, 2 per cent.; myelitic and polyneuritic, 24.5 per cent.; myelitic and bulbar, 18.3 per cent.

In forty-two of these forty-nine patients a study of the cerebrospinal fluid by means of the colloidal gold test was made, a total of 132 spinal fluids being thus examined. These fluids were removed at intervals ranging from the fourth to the eighty-fourth day of illness, 107 fluids being obtained in the first six weeks.

Divided according to the respective weeks in which they were taken, the fluids were distributed as follows:

First week	14 fluids	Seventh week	11 fluids
Second week	21 fluids	Eighth week	6 fluids
Third week	16 fluids	Ninth week	3 fluids
Fourth week	21 fluids	Tenth week	2 fluids
Fifth week	21 fluids	Eleventh week	2 fluids
Sixth week	14 fluids	Twelfth week	1 fluid

---

* Received for publication, Oct. 23, 1922.

* From the Kingston Avenue Hospital, of the Bureau of Hospitals, Department of Health, New York City; Dr. R. J. Wilson, director, and Dr. William T. Cannon, resident physician.

1. Regan, J. C., and Cheney, G. W. H.: Amer. J. Dis. Child. **23**:107 (Feb.) 1922.

The following results were obtained:

1. *Zone in Which the Poliomyelitic Reduction Occurs.*—In no instance was a normal reaction encountered in any poliomyelitic fluid taken during the first few weeks, or in what is to be considered as the very acute period of the disease. The type of reduction found was constantly in the same zone, the zone of low dilutions, the so-called syphilitic zone. A characteristic type of reduction in the first week or two is 11½22100000. In ninety-one of the 132 spinal fluids the reaction was limited to the first five dilutions (from 1:10 to 1:160) and fell strictly within this zone. In twenty-six of the remaining fluids it extended into the sixth dilution (1:320) and in twenty-two of these twenty-six instances the reading was either 0½ or 1, and hence practically negligible. In thirteen of the remaining fourteen fluids the reaction reached the seventh dilution (1:640) and in one fluid the eighth dilution. In other words, in more than 68 per cent. of the spinal fluids, the reduction of colloidal gold was limited to dilutions of from 1:10 to 1:160, and in 88 per cent. to dilutions of from 1:10 to 1:320.

In ten cases of the forty-two, the reaction extended beyond the sixth dilution, but commonly this extension occurred during the earlier period of the disease, and in all instances except two it was limited to a 0½ or 1 reduction. The type of the disease in such patients has commonly presented certain characteristics, that is, the polyneuritis was marked, or occasionally meningitic symptoms were pronounced, or extensive paralysis existed. It would seem, in general, then, that in acute poliomyelitis the colloidal gold chlorid reaction is rather sharply limited to dilutions of from 1:10 to 1:320, with the exception of certain patients who presented marked polyneuritis or meningitic symptoms.

2. *Variations of the Height of the Reaction at Various Periods of the Disease.*—By summarizing the total number of curves in the various weeks and taking a mean average, it was found that the average curve is highest in the first and second weeks, and then gradually declines reaching an almost normal level by the eighth week.

It is to be noted that the average curve for the respective weeks was slightly lower in the present series than in the previous series.

3. *Description of the Average Reactions in the Various Weeks.*—In the first week the reduction encountered in this series started in the red blue in 1:10 extended into the lilac or purple in from 1:40 to 1:80, and descended somewhat more abruptly into the reddish blue color in 1:160, reaching the nonreducing red again in 1:320. In the second week, the curve was very similar; in the third week, there was a slight lowering in the height of the curve. In the fourth week, there was a

decided change and the reaction fell entirely in the red blue from 1 : 10 to 1 : 160. In the sixth week, the red blue was reached only in from 1 : 40 to 1 : 80, and finally in the eighth week the average reaction was entirely confined to the normal nonreducing red color. Figure 1, curves *a, b, c, d,* show the type of average curve obtained in the first, third, fifth and seventh weeks, respectively.

4. *Time of Disappearance of the Positive Reaction in the Different Cases.*—One patient showed a normal reaction as early as the third week; four patients had a normal reaction in the fourth week, three in the fifth week, three in the sixth week, two in the seventh week, and two in the eighth week. Thus of the spinal fluids of twenty-three patients examined up to or beyond the eighth week, fifteen, or 65 per cent., presented a normal reaction by this time. In this connection, it is to be noted that only 30 per cent. of the cases in the first series showed a normal reaction by the eighth week.

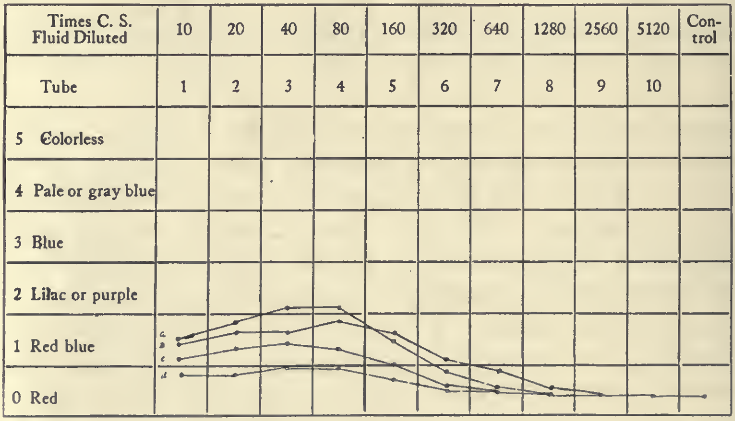


Fig. 1.—Average curves for the first (a), third (b), fifth (c), and seventh weeks (d) of the disease.

Of the eight patients with a positive reaction reaching to the eighth week or beyond, the last puncture was performed in the eighth or ninth week and found still positive in five cases, and negative in one case, while of the remaining two cases one became negative in the eleventh week, and the other still persisted positive when the last fluid was taken in the eleventh and twelfth weeks, respectively.

Hence, it seems that in poliomyelitis the colloidal gold test rarely reaches normal before the end of the third week, and that in one half of the cases it continues elevated still at the end of the eighth week, persisting when all other pathologic changes in the spinal fluid have commonly disappeared.

5. *The Relation of the Type of the Disease to the Subsidence or Persistence of the Positive Colloidal Gold Reaction.*—(*a*) These cases with an early subsidence of the positive reaction from the third to the seventh week, were characteristically mild types of poliomyelitis in which polyneuritis, if any had been present at all on admission, rapidly disappeared, the paralysis quickly improved, or vanished, and the child became convalescent early and made an excellent recovery. (*b*) It was commonly the more severe cases with extensive and slowly improving paralysis and with moderate or marked neuritis in whom the curve remained elevated to the eighth week and beyond.

6. *Reactions in Fatal Cases.*—The type of reduction in the spinal fluids of four fatal cases examined was very much like that found in the nonfatal cases in the first week of the disease.

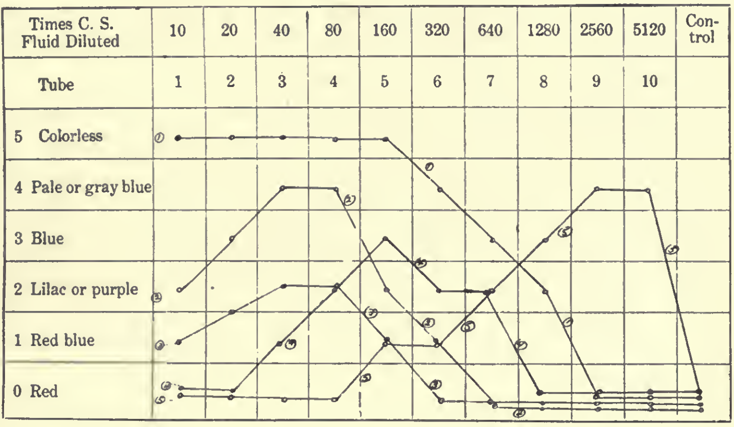


Fig. 2.—Comparative curves in various diseases: (1) General paresis, 5 5 5 5 5 4 3 2 0 0; (2) cerebrospinal syphilis, 2 3 4 4 2 1 0 0 0 0; (3) acute poliomyelitis, 1 1½ 2 2 1 0 0 0 0 0; (4) tuberculous meningitis, 0 0 1 2 3 2 2 0 0 0; (5) epidemic cerebrospinal meningitis, 0 0 0 0 1 1 2 3 4 4.

7. *Relationship Between the Cytology and Chemistry of the Spinal Fluid and the Colloidal Gold Reaction.*—(*a*) The amount of globulin has borne no relationship to the height of the colloidal gold curve. Often a high curve would be accompanied by a low or absent globulin reduction, or vice versa, a high globulin reduction would be found with a low curve. The presence or absence of globulin in the spinal fluid has borne no definite relationship to the positive or negative gold chlorid reaction.

(*b*) There was no definite relation between the height of the gold chlorid curve and the number of cells per cubic milimeter in the spinal fluid. However, as the weeks of the disease passed, and the cell count decreased, the gold chlorid reaction subsided, but this latter was much slower in its decline, and in the majority of cases remained elevated for a period of several weeks after the cell count had reached normal levels, which occurred in this series between the second and third weeks.

8. *Value of the Reaction in the Diagnosis of Poliomyelitis.*—Certain diseases have a reaction in the same zone as poliomyelitis. These diseases may be divided into several groups: (1) Various forms of syphilis of the nervous system—tabes dorsalis, syphilitic meningitis, gumma of the brain, etc. (2) Various forms of insanity—dementia praecox, senile psychosis, paranoia, maniac depressive insanity, imbecility, alcoholic psychoses, etc. (3) Acute encephalitis due to various infectious causes, and brain abscess. (4) Postdiphtheritic paralysis. These first four groups give quite constantly reactions in dilutions of from 1:10 to 1:160 or 1:320 and similar grades of precipitation as seen in poliomyelitis. (5) Then there is a fifth group including diseases which occasionally are said to give reactions in this zone—epilepsy, spinal cord tumor, chorea, multiple sclerosis, edema from sunstroke, tuberculous meningitis and epidemic encephalitis.

The differential diagnosis of poliomyelitis from these diverse conditions cannot be discussed here in detail. A few salient points, however, will be pointed out. The differentiation of poliomyelitis from syphilitic diseases of the nervous system should offer no difficulties. The history, symptoms and other laboratory data, including the Wassermann reaction, will be sufficient to establish the diagnosis. It is very essential in the case of all poliomyelitic fluids tested with colloidal gold also to make a spinal fluid Wassermann test. This precaution was carried out in the present series.

The various forms of insanity certainly cannot be confused clinically with poliomyelitis. It is only the encephalitic form of poliomyelitis which would likely be confused with an acute encephalitis and this form is relatively rare.

Postdiphtheritic paralysis is commonly readily recognized by the history of a previous angina, by the more gradual afebrile, or practically afebrile, onset, the localization of the paralysis in certain characteristic muscles (soft palate, extrinsic or intrinsic muscles of the eye, etc.), and the absence of a meningeal syndrome of onset. The lack of any increase of cells in the spinal fluid, and the rapid improvement with eventually complete disparition of the paralysis without atrophy will almost always settle a question of differential diagnosis.

Epilepsy, spinal cord tumors, chorea, and multiple sclerosis are clinically not to be confused with poliomyelitis, unless under exceptional circumstances.

Tuberculous meningitis in its early stages gives, at times, a reaction in the lower dilutions resembling, then, somewhat a poliomyelitic reduc-

Partial Brief Summary of Cases with Spinal Fluid Examinations *

Case No.	Date of Onset	Age	Cerebrospinal Fluid Examinations				Paralysis on	
			Date Taken	Globulin	Cells per C.Mm.	Colloidal Gold Reactions	Admission	Discharge
1849	9/18	15 mo.	9/24	0	17	1 1½2 2 1 0 0 0 0 0	Bulbar and right lower	Died
1909	10/ 3	5 yr.	10/10	0	80	1 1 1 1½1 1 0 0 0 0	Bulbar	Died
1742	8/26	4 yr.	8/30	0	10	1 1½2 2 1½0 0 0 0 0	Bulbar	Died
1951	10/13	20 mo.	10/22	1+	35	1 1½2½2 1 ½0 0 0 0	Left lower	Weakness left foot
			11/ 7	0	12	0 0 0 0 0 0 0 0 0 0		
2031	10/27	4 yr.	11/ 9	0	10	1 1 1 1½1½0 0 0 0 0	Neck, back and weakness lower extremities	None
			11/17	0	5	1 2 1 1 1 0 0 0 0 0		
			12/17	0	0	0 0 0 0 0 0 0 0 0 0		
1999	10/27	4 yr.	11/ 1	0	120	½1 1 ½ ½ ½0 0 0 0	Neck, left facial, tongue	Slight left facial
			12/ 2	0	0	0 0 0 0 0 0 0 0 0 0		
1786	8/26	2 yr.	9/27	1+	112	3 2½ ½2 2½1 0 0 0 0	Neck, back and lower extremities	Partial, both lower
			9/30	0	50	1 1½2 1 0 0 0 0 0 0		
1589	7/ 9	8 yr.	7/21	1+	24	1 1 1 2 3 3 3 0 0 0	Back, left arm and both lower	Partial, both lower
			7/24	1+	60	1 2 2 3 3 3 3 2 0 0		
			9/15	?	?	0 0 0 0 0 0 0 0 0 0		
1764	8/31	2½ yr.	9/ 8	0	5	1 1 2 1½1 ½0 0 0 0	Neck, back and both lower extremities	Complete left lower and weak right lower
			10/24	0	0	1 1 1 ½0 0 0 0 0 0		
1780	9/ 1	17 mo.	9/ 9	0	10	2 2 1½1 1 ½0 0 0 0	Right lower	Partial right lower
1663	7/14	3 yr.	8/12	1+	0	½ ½1 2 0 0 0 0 0 0	Back, right upper and right lower	Slight weakness right lower
			8/26	0	0	0 0 0 0 0 0 0 0 0 0		
1819	9/10	2 yr.	10/ 4	0	37	1 1 2 1 1½0 0 0 0 0	Right lower	Partial right lower
			10/23	0	5	1 1 1 1½1 0 0 0 0 0		
1824	9/16	2 yr.	10/ 3	0	42	½1 1½2 2 1½1½0 0 0	Back, neck, both upper and both lower extremities	Both upper and lower extremities
			10/11	0	180	1 2½2 1 ½0 0 0 0 0		
			10/13	0	20	1 1 1 2 2½0 0 0 0 0		
			10/27	0	5	1 1 2 0 0 0 0 0 0 0		
1802	9/10	15 mo.	10/ 4	0	135	1 1½2 2 2 1 0 0 0 0	Right lower and partial right upper	Partial right lower
			10/13	0	15	1 2½1½ ½ ½ ½0 0 0 0		
			10/23	0	7	1 1½1 ½0 0 0 0 0 0		
1885	9/28	3½ yr.	10/ 5	0	65	½1 2 2 ½0 0 0 0 0	Soft palate and slight deglutit.	Slight palatine
			10/13	0	0	1 ½ ½ ½0 0 0 0 0 0		
1861	9/20	2 yr.	10/ 4	0	15	1 2 1½1 ½0 0 0 0 0	Partial both lower extremities	Weakness both lower extremities
			10/13	0	17	0 0 0 0 0 0 0 0 0 0		
			10/23	0	2	0 0 0 0 0 0 0 0 0 0		
1615	7/12	3 yr.	8/16	1+	4	1 2½2 2 ½0 0 0 0 0	Partial both upper and lower extremities	Partial right upper
			8/25	1+	0	½1 1 2 1 0 0 0 0 0		
			9/ 6	0	5	0 0 0 0 0 0 0 0 0 0		
1897	10/ 2	11 yr.	10/12	1+	12	1 1 2 3 2 ½0 0 0 0	Back, left lower and partial right lower	Weakness right lower and partial left lower
			10/20	1+	10	1 1 1½1½2 2 0 0 0 0		
			10/26	1+	15	½1 1½ ½ ½0 0 0 0 0		
			11/15	1+	0	0 0 0 0 0 0 0 0 0 0		
1947	10/16	3 yr.	10/20	0	40	1½2 2 2 1½1 1 0 0 0	Right lower extremity	Weakness right lower
			10/28	0	32	½1½2 1½0 0 0 0 0 0		
			11/ 3	0	2	1 1 1 ½ ½0 0 0 0 0		
			11/ 9	0	5	0 0 0 0 0 0 0 0 0 0		
1820	9/10	10 mo.	10/ 6	0	85	2½1 2 ½ ½0 0 0 0 0	Neck, back partial both lower	Partial left lower
			10/13	0	12	1 1 2 2 1 0 0 0 0 0		
			10/20	0	0	1 1 1 1 0 0 0 0 0 0		
1911	10/ 5	1 yr.	10/12	0	45	2 3 2½1 ½0 0 0 0 0	Left lower extremity, left upper extremity	Partial left lower and upper
			10/27	2+	12	1 1 1½2 0 0 0 0 0 0		
			10/31	0	5	½ ½ ½1 ½ ½0 0 0 0		
			11/ 7	0	0	0 0 0 0 0 0 0 0 0 0		
1724	8/15	16 mo.	12/ 1	0	6	1 1 2 2 1½ ½0 0 0 0	Neck, back, diaphragm, right upper, bases of lungs	Partial right upper
			12/15	0	7	1 1 1 1½0 0 0 0 0 0		
			12/28	0	0	½1 1 1 1 0 0 0 0 0		
			12/30	0	0	0 0 0 0 0 0 0 0 0 0		
2010	10/24	9 yr.	11/ 1	2+	15	1 1 1 2 2 2 0 0 0 0	Both lower and partial back	Partial right lower and weakness left lower
			11/29	1+	1	1 1 2 3 2 2 0 0 0 0		
			12/24	0	0	0 ½ ½1 2 0 0 0 0 0		

---

* Owing to lack of space only a partial summary of the cases with spinal fluid findings could be included.

tion. But as the disease develops, the curve is prolonged out into the meningitic zone. In the early stages there are also the history, symptoms and the other spinal fluid findings, including cell increase, globulin and sugar reductions. The cell increase is apt to be greater, the globulin higher, and the sugar reduction less in tuberculous meningitis. Moreover, tubercle bacilli may be found.

Epidemic encephalitis, according to the small number of reports made on the subject, gives a colloidal gold reaction of a variable type.[2] In a considerable number of cases it is said to be negative, while in others a reaction of a paretic, meningitic or syphilitic type is encountered. Accordingly, it may be said that while a syphilitic type of reaction may occur in epidemic encephalitis and in poliomyelitis, a negative, a paretic or meningitic type of curve is encountered only in the former. Obviously, the clinical picture of the two diseases is quite distinctive, and there are a great many clinical points on which a differential diagnosis is usually readily based. The same may be said of any acute encephalitis and also of brain abscess. Another point is, that the cytologic and, at times, chemical reactions are more commonly absent in this condition than in poliomyelitis.

Meningismus due to various diverse causes—gastro enteritis, pneumonia, acute infections, etc., is seldom accompanied, in our limited experience, by a spinal fluid which produces marked reduction of colloidal gold. If any reaction occurs it is usually so slight as to be negligible.

The importance of the colloidal gold reaction in epidemic poliomyelitis, may be overlooked if it is forgotten that other positive findings in the augmentation of cells and globulin may be very slight, slightly beyond normal, and may be entirely absent after the first several days of the disease have passed. It is in such instances that the constancy of a syphilitic type of curve is especially of assistance in diagnosis.

SUMMARY

In a series of forty-two cases of acute poliomyelitis, including 132 spinal fluids, a study of the colloidal gold reaction was carried out. The spinal fluids were obtained at various intervals from the fourth to the eighty-fourth day of the disease.

CONCLUSION

The following conclusions were drawn from the results obtained in this and a previous series of cases.

---

[2] Tilney, F., and Howe, H. L.: Epidemic Encephalitis, New York, Paul Hoeber, 1920, p. 105.

1. There was always a reaction with colloidal gold solution in the case of every poliomyelitic fluid taken during the acute stage of the disease.

2. This reduction was constantly in the same zone—the zone of low dilutions, the so-called syphilitic zone. In 88 per cent. of the spinal fluids examined, the reaction occurred in the first six dilutions between 1:10 to 1:320.

3. In fourteen spinal fluids the reaction extended to the seventh dilution (1:640). These patients more or less characteristically presented marked polyneuritic or meningitic symptoms, or else pronounced paralysis.

4. The average curve or reaction showed very similar characteristics in the first and second weeks of the disease. A gradual decline in the curve was then observed.

5. In no instance was a normal reaction encountered before the end of the third week of illness.

6. In twenty-three patients the spinal fluid was examined as late as the eighth week, and fifteen, or 65 per cent., had become normal by that time.

7. Cases in which a normal reduction returned early, from the third to the seventh week, were mild types of the disease, while those in which the curve remained elevated beyond the eighth week had usually polyneuritis or extensive and slowly improving paralysis or both.

8. The reaction showed no distinctive points in the fatal cases, and, therefore, was of no value in prognosis in this regard.

9. The positive reaction bore no constant relation to the presence of globulin in the spinal fluid, nor to its disappearance.

10. There was no close ratio between the number of cells per cubic millimeters in the spinal fluid and the test, but as the cell count decreased, the colloidal gold curve subsided, somewhat more slowly, however, remaining elevated for several weeks after the cell count was normal.

11. With the subsidence of the colloidal gold reaction there is usually concomitantly an accompanying improvement in the patient's general condition, the paralysis, the meningitic symptoms and the polyneuritis. In fact, it would seem that the return of a normal reduction of colloidal gold indicates approximately the end of the acute stage of the disease. As this coincides with the improvement observed clinically, this termination of the acute stage can readily be determined by watching the symptoms. The colloidal gold reaction is naturally not to be used as a routine to determine this.

12. In differential diagnosis the colloidal gold reaction should be utilized in conjunction with the history, symptoms and other laboratory

data, and thus employed it is one of the most valuable tests we have for the recognition of the disease. While its significance is possibly not quite as great, it is far more constant and persistent than either the cell or globulin increase. Its possible use in the preparalytic stage of the disease must not be forgotten.

We wish to acknowledge the excellent assistance given by Miss Helen Meyers, of the laboratory staff, in the performance of the laboratory portion of the work.

American Journal of Diseases of Children

Vol. 25 FEBRUARY, 1923 No. 2

THE INFLUENCE OF GROWTH ON THE BASAL METABOLISM OF CHILDREN *

G. B. FLEMING, B.A., M.D.

GLASGOW, SCOTLAND

The total metabolism of the growing child is universally admitted to be proportionately higher than that of the adult, and Benedict and Talbot[1] have shown that the basal metabolism is also considerably raised during the growth period. From their numerous observations it has been possible for them to provide us with figures showing the expected basal metabolism for any age. Although the basal metabolism for any age is fairly constant, it is probable that the difference between the basal and total metabolism varies considerably in different persons. This variation is probably due to differences of temperament and environment. The active, highly strung boy has a higher metabolism than the lethargic boy. In considering the total food requirements two other factors have to be included. These are: (1) the energy lost in the excreta (feces and urine). In neither of these excreta has complete combustion taken place, and they contain a certain caloric value. The amount lost by this means is about 10 per cent. of the total requirements. (2) The energy expended in growth.

Both Talbot[2] and Holt[3] allow during the first year of life, in addition to the basal requirements, about 45 calories per kilogram for growth; but this seems to be far too much. It must be remembered that the subject while in the respiratory chamber or calorimeter is, as far as we know, growing just as much as when he is lying in bed, consequently, when apportioning the difference in calories between the total and basal requirements, the heat expended in manufacturing new tissue is included in the basal heat output, and only the amount of tissue actually added to the body in growth has to be included under the growth heading.

In the first six months of life a normal infant doubles its weight. Presuming the proportionate composition of its body to be the same at

---

* Received for publication, Dec. 1, 1922.

* From the Royal Hospital for Sick Children.

[1] Benedict and Talbot: Carnegie Institute of Washington Publications, Washington, D. C., 1914, 1921.

[2] Talbot, F. B.: Woman's Milk, Am. J. Dis. Child. **18**:229 (Sept.) 1919.

[3] Holt, L. E., and Fales, H. L.: Food Requirements of Children, Am. J. Dis. Child. **21**:1 (Jan.) 1921.

birth as it is at 6 months, then the total number of calories added to its body in six months will be equal to the caloric value of the new-born child. From the analyses made by Camerer and Soldner[4] of new-born infants I have calculated that at birth an infant's body has a caloric value of approximately 5,000. If it doubles its weight in six months, then it will have added to its body tissue a value of 5,000 calories, that is, about 27 calories a day and an average of about 5 calories a day per kilogram, taking its mean weight during the first six months of life to be 5 kilograms. It is, therefore, only this amount of the surplus requirements above the basal which can be accounted for by growth.

These considerations show that the basal metabolism during the growth period represents not only the energy expended in carrying on the ordinary vital processes during repose but also a certain quota expended in manufacturing new tissue. Is it possible that the high basal metabolism of this period can be accounted for by this? Unfortunately, two other factors confound the issue. In children under 3 years of age, it is impossible to estimate the basal metabolism in the post-absorptive state, consequently the specific dynamic action of the food exalts the basal metabolism rate to some extent, probably not more than 10 per cent. Secondly, in children there is a much greater proportionate body surface than in adults. This, according to Rubner's law, should cause an increase in the metabolism when compared to body weight. But Benedict and Talbot[1] have shown that the metabolism of the child does not obey Rubner's law, and from their figures it is clear that the high basal metabolism cannot be caused entirely by relatively increased body surface. It seems probable that neither of these two factors can account for the entire increase in basal metabolism, and probably the energy expended in making new tissue plays an important part.

Wilson[5] and Rubner[6] agree that for a lower animal to construct 1 kilogram of normal body substance, it requires an ingestion of about 4,700 calories in food, and Rubner states that for man six times this amount is necessary. That is to say, for a child to add 1 kilogram to its weight 28,200 calories are required and to add 3.5 kilograms, which it does in six months, 98,700 calories are necessary; that is, an average of 548 calories per day. Rubner also considers that in the growing human being 5.2 per cent. of the calories in the diet is retained in the form of new tissue. That is an average of 27 calories per day during the first half year of life.

---

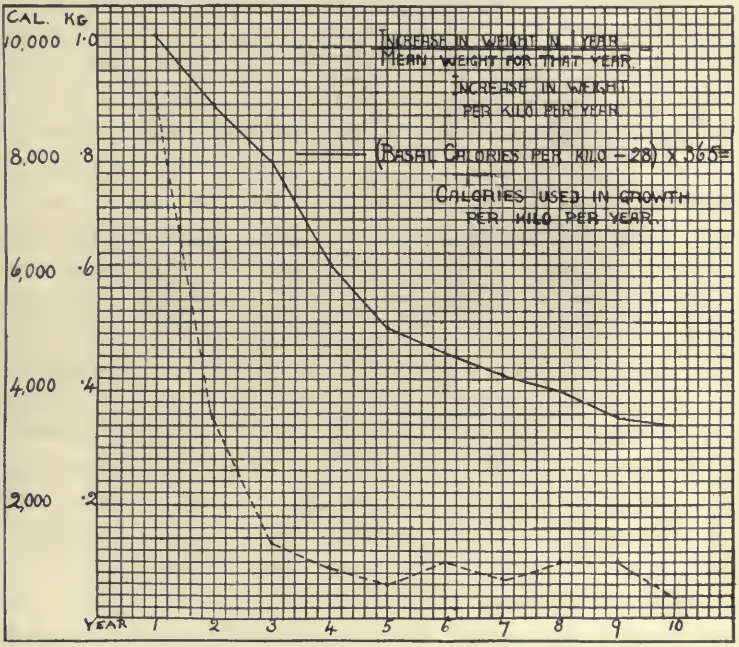
[4] Camerer and Soldner, quoted by von Noorden: Metabolism and Practical Medicine, London, W. Heinemann, 1907.

[5] Wilson, cited by Lusk: The Science of Nutrition, Philadelphia, 1919.

[6] Rubner: Das Problem der Lebensdauer und Seiner Beziehung zu Wachstum und Ernährung, München, 1908.

Unfortunately, neither the calculations of Wilson nor those of Rubner help us to determine how much of the basal heat output is devoted to the manufacture of new tissue for, as explained above, it is probably from the basal heat output that this energy is derived.

We know, however, that in the adult the basal metabolism is about 28 calories per kilogram. Is it possible that in the child the excess over this figure can be accounted for largely by the work done in manufacturing new tissue? The specific dynamic action of food and the relatively large surface area of the child no doubt complicate the proposition, and on account of this it does not seem possible to say definitely how much energy is expended in growth.



Yearly increase in weight of a normal child per kilogram for the first ten years of life.

The accompanying chart shows the yearly increase in weight of a normal child per kilogram for the first ten years of life $\left(\frac{\text{increase in weight for one year}}{\text{mean weight for that year}}\right)$ and the daily basal metabolism per kilogram minus 28 and multiplied by 365 for each year of life up to 10 years of age. Then, 28 is subtracted from the daily basal metabolism per kilogram, as 28 calories may be taken as the basal figure for adults, and the total basal heat output of a child per kilogram per day minus 28 will give the number of calories per day, and multiplied by 365 will give the number per year that we wish to account for.

Though these two curves do not correspond very closely, especially in the first two years of life, they both show the same tendency to flatten out as age increases and the rate of growth decreases, and seem to afford a certain amount of evidence in favor of the suggestion that the high basal metabolism of the growing child may to some extent be accounted for by the amount of energy expended in the manufacture of new tissue.

NEUROPSYCHIATRIC SEQUELAE OF ACUTE EPIDEMIC ENCEPHALITIS IN CHILDREN *

FRANKLIN G. EBAUGH, A.B., M.D.
Director of the Neuropsychiatric Department of the
Philadelphia General Hospital
PHILADELPHIA

In reviewing the enormous number of articles on all phases of acute epidemic encephalitis one cannot help being impressed by the lack of attention paid to children who have suffered from this disease. This is especially true of the important neuropsychiatric sequelae. Few articles deal exclusively with acute epidemic encephalitis in children. Happ and Blackfan,[1] Happ and Mason,[2] Grossman,[3] Leahly and Sands,[4] and recently Hohman [5] have written on this subject, the two last named having confined their remarks to the psychiatric manifestations of this interesting and protean disease.

During the past few months seventeen patients have been referred to the neuropsychiatric clinic for examination, because of marked behavior abnormalities. Many of these patients were referred directly by the school authorities because they had been unmanageable and unable to progress in school. Frequently, they had disturbed the whole class, since they were very quarrelsome and impulsive and often left the school building during class exercises. Nor did these children respond to discipline. Other children were referred by their parents with complaints of equally serious character. In two cases marked sexual precocity was exhibited. In another case, the patient attempted to kill other members of his family. Other children were brought to the clinic for follow-up care after the acute manifestations of the disease had terminated in the hospital. These cases gave us additional opportunity to study the whole course of the disease, especially the neuropsychiatric sequelae.

---

* Read before the New England, New York and Philadelphia pediatric societies, Nov. 4, 1922.

* Received for publication, Nov. 19, 1922.

* From the Neuropsychiatric Clinic, Philadelphia General Hospital.

[1] Happ, W. M., and Blackfan, K. D.: Insomnia Following Acute Epidemic (Lethargic) Encephalitis in Children, J. A. M. A. **75**:1337 (Nov.) 1920.

[2] Happ, W. M., and Mason, V. R.: Epidemic Encephalitis, Bull. Johns Hopkins Hosp. **32**:137 (May) 1921.

[3] Grossman, M.: Late Results in Epidemic Encephalitis, Arch. Neurol. & Psychiat. **5**:580 (May) 1921.

[4] Leahly, S. R., and Sands, I. J.: Mental Disturbances in Children Following Epidemic Encephalitis, J. A. M. A. **76**:373 (Feb. 5) 1921.

[5] Hohman, L. B.: Postencephalitic Behavior Disorders in Children, Bull. Johns Hopkins Hosp. **33**:120 (Oct.) 1922.

This group consisted of six girls and eleven boys. The age varied from 2 to 14 years. The lapse of time since the subsidence of the acute symptoms of encephalitis is as follows: in four cases, three or more years; in two cases, two or more years; in five cases, from one to two years; and in seven cases, less than one year.

PSYCHIATRIC SEQUELAE

The psychiatric sequelae consist mainly of the following psychopathologic trends:

Total Change in the Patient's Character and Disposition.[6]—This was present in ten of the children (Cases 2, 3, 4, 5, 10, 12, 13, 14, 15 and 16). Normal children who were well adjusted in school and home changed abruptly to a state of hyperkinesis, characterized by transient periods of talkativeness, tension states and emotional outbreaks often leading to general incorrigibility and inability to remain in school. These children were uniformly restless and overexpressive in their activities. They showed marked emotional lability consisting of capricious moodiness, irritability and affability, leading to quarrelsomeness and often overaffectionateness. These behavior trends appeared to be fairly constant in these cases. Owing to their behavior abnormalities it was necessary to keep these ten children out of school. Three of them required prolonged hospital stay during their periods of excitement. One of these patients, a girl, aged 10, was difficult to manage. She was noisy, abusive to other children and capriciously depressed. She was "bossy," quick tempered, and impulsive and showed little respect for authority. This patient was also overaffectionate and before admission to the hospital had accosted men on the streets. She gave evidence of definite sexual precocity. One boy had streaks of cruelty, and on one occasion stabbed a schoolmate with a knife. Another boy, who formerly had been quiet and orderly, became obscene and masturbated in public. He was silly and sang love songs for prolonged intervals. The acuteness of this behavior change necessitated his admission to the psychopathic ward.

In the remaining seven children there was not an abrupt change in character. Some gave a history of previous behavior difficulties, probably due to lack of careful home training regarding habit formation. Two of the six children already had a record of incorrigibility. Another child gave evidence of an hysterical make-up and reacted to unpleasant situations by developing many complaints. For example, he became deaf when told to do anything unpleasant. One boy, previously difficult to manage at home, had sudden outbreaks of violence and on one occasion attempted to kill his sister. He also showed sexual precocity.

---

[6] Francioni, R.: Changes in Character and Mind After Epidemic Encephalitis, Policlinico **28**:575 (April) 1921.

He frequently kissed girls whom he met on the street and on one occasion attempted intercourse. He became vagrant and went to sleep on doorsteps in the early morning hours after walking the streets all night. In each of these children the sequels of the disease consisted in a marked accentuation of their former behavior abnormalities. Three patients did not show any behavior abnormalities after the acute disease terminated.

Nocturnal Restlessness and Insomnia.—Insomnia following encephalitis in children has been a fairly constant finding. This inability to sleep until the early morning hours, often as late as from 3 to 5 o'clock, is followed by sleep into the forenoon. The insomnia is accompanied by motor restlessness. One boy spent many hours talking, singing, whistling, thrashing about in his bed, and fighting with his pillow. It is of interest to note that persistent insomnia rarely occurs in children suffering from other diseases. It is usually seen after an acute infectious disease and occurs in severe types of chorea. Insomnia is one manifestation of a neurotic condition in a child. I agree with the observation of Happ, Blackfan and others,[7] that insomnia is a common sequela of acute encephalitis in children.

Affective Disorders.—Affective disorders have already been referred to as an important part of the change in disposition occurring in children after the acute stage of the disease has terminated. Of three children who showed depressive tendencies, one boy attempted suicide by drowning, while another boy stated that he "was no good" and threatened to kill himself with a gun. He spoke of feeling "heavy hearted." Another boy attempted suicide by choking himself with a handkerchief while in the psychopathic ward. In each case there was no real desire to commit suicide. The affect change was not clear cut and decisive as is the rule in depressive reactions, nor was there the characteristic slowness of thinking and planning. Hohman [8] has previously noted similar findings in adults, in whom the affective changes occur more frequently than in children. The emotional instability present in the other cases under consideration is analogous to that seen in organic reactions.

Hysterical Reactions.—In three of our patients marked hysterical phenomena were observed. One child developed spells of the functional variety, usually to escape from a difficult situation. The spells consisted of prolonged periods of rapid respirations, the child thus feigning illness in order to stay out of school. There was no history of hysterical make-up before this boy developed encephalitis. Another boy developed

---

7. Naville, F.: The Mental Complications and Sequelae of Acute Epidemic Encephalitis, Encéphalé **17**:423 (July) 1922. Rütimeyer, W.: Postencephalitic Insomnia, Schweiz. med. Wchnschr. **51**:7 (Jan. 6) 1921.

8. Hohman, L. B.: Epidemic Encephalitis (Lethargic Encephalitis), Arch. Neurol. & Psychiat. **6**:295 (Sept.) 1921.

FINDINGS IN ENCEPHALITIS CASES *

Name	Age	Onset	Symptoms	Psychiatric Sequelae	Neurologic Sequelae	Results
1 Maud N.	12	Sept., 1919	Influenza, headaches, dizziness, diplopia, insomnia, ptosis	Nocturnal restlessness, increase in activity during daytime	Choreiform movements	Improving, now attends school; choreiform movements disappeared
2 Jessie M.	10	Feb., 1919	Fever; acute delirium; lethargy 3 weeks; visual disturbances	Restless, overactive, incorrigible, sexual precocity	Choreiform movements; endocrine disturbance of hypopituitary type	No improvement
3 Edith S.	6	Jan., 1919	Influenza, delirium; lethargy 5 days	Mental deficiency; imbecility; agitated, restless	Twitchings during sleep	No improvement; no signs of mental development since onset
4 Nathan D.	10	April, 1920	Acute delirium; diplopia; facial twitching; insomnia	Total change in disposition and character, noisy, abusive, destructive, impulsive, untruthful, hysterical attacks, threatened suicide; odd behavior (begs on street); many fears; tics	Irregular respiratory movements; internal strabismus; oversalivation	No improvement; taken from school; admitted to psychopathic ward
5 George McK.	6	Nov., 1920	Fever, jaundice, delirium; lethargy; twitchings	Extreme overactivity, especially nocturnal, with insomnia; became obscene, destructive, unmanageable	Internal strabismus	Improving
6 Peter A.	13	Feb., 1921	Acute delirium, headaches, diplopia	Always incorrigible; extreme insomnia, irritability, impulsiveness, quarrelsomeness; depressive reaction; attempted, 12/1921, to drown himself; hysterical outbreaks; behavior abnormalities contributed to commitment to reform school	Sluggish irregular pupils; internal strabismus; marked salivation	Transient improvement following spinal drainage; incorrigibility decreasing and insomnia decreasing
7 George B.	10	Feb., 1921	Headaches, convulsions; delirium; diplopia short period; lethargy	Periods of excitement; attempted to jump from window; streaks of cruelty; tried to stab another boy; bossy, domineering; increased hysterical tendencies	Oversalivation; irregular pupils	Slow improvement, still unstable
8 Victor La M.	8	Jan., 1921	Headaches, diplopia, delirium; prolonged lethargic period	Incorrigibility before illness showed marked increase; overactive, quarrelsome, antagonistic; attempted to kill brothers and sisters; impulsive; kisses girls on street; vagrant; sexual precocity leading to court commitment	None	Normal behavior during hospital residence; home conditions bad; change in environment and occupational therapy have helped

9 Warren S.	8	June, 1921	Headaches; shooting pains of arms and legs; twitchings; diplopia; delirium; choreiform movements	No behavior abnormalities......................	Choreo-athetoid movements of left arm; typical chorea of left arm and leg; oversalivation; left side facial weakness, masklike expression; rigidity of left side body	Not seen after discharge from hospital; relative reports improvement after osteopathy
10 Dora O.	10	Feb., 1921	Acute illness followed by lethargic condition 16 days	Numerous behavior abnormalities, marked hyperkinesis leading to general incorrigibility; precocious sex characteristics; vagrancy; placed in O.B. class	None	Doubtful improvement; behavior abnormalities continue; no improvement after hospital care
11 John R.	8	June, 1922	Convulsion, fever; twitching; spinal fluid findings positive; insomnia, nocturnal restlessness	No behavior abnormalities after acute illness cleared up	Bilateral twitching of temporal muscle; oversalivation	Well; improvement after spinal drainage
12 Sophia J.	8	March, 1922	Dizziness, headaches, earache; delirium; lethargy 2 weeks duration	Manic-like reaction, continuously wandered about room; overaffectionate	Weakness, right external rectus; nystagmoid movements; ptosis; facial weakness on left side	Continued incorrigibility; taken from school
13 Ernest S.	13	May, 1922	Marked abdominal pain, headache; lethargy 1 week	Became silly, obscene, masturbated in public; vagrant; many fears	Mild optic neuroretinitis	Return to school; improving; spinal drainage a factor
14 George McD.	8	March, 1922	Ptosis, diplopia, delirium, insomnia	Odd antics at night, fights with pillows for prolonged intervals; sleeps till noon; overactive	Irregular pupils; left internal strabismus; occasional choreiform movements	Little improvement; insomnia; medication; hydrotherapy ineffectual
15 Charles K.	14	Feb., 1922	Headaches, dizziness, radiculitis, diplopia, masseter tenderness, nocturnal restlessness	Threatened suicide because of "heavy heartedness"; insomnia; frequent masturbation	Frequent headaches	Marked improvement after spinal drainage; working (bell boy)
16 Dorris F.	2	April, 1922	Acute illness characterized by eyes crossing and total absense of mental development since	Overactive, irritable, whiny, fussy; typical picture of idiot; normal development before	Strabismus, choreiform movement of both arms; movement of head	Evidently permanent sequelae
17 Isadore L.	3½	Feb., 1919	Normal birth, slept continually for 8 days; on being fed, immediately fell asleep, followed by inability to sleep for 11 weeks; cried continually; has shown no mental development since; mother had influenza in middle pregnancy, other siblings normal except one, who evidently had a meningitis during infancy followed by mental retardation	No evidence of mongolianism................	Typical idiocy	If encephalitis, belongs to permanent mental deficiency residual

---

* Cases are presented in schematic form to show symptoms, onset, psychiatric and neurologic sequelae, as well as the present condition of the patient. In all cases, a diagnosis of "encephalitis" was made by exclusion. Wassermann reactions, as well as other laboratory reports, were negative in all cases unless noted.

spells of screaming and yelling to avoid the discipline of a correctional school. Another boy, previous to the attack of encephalitis, had shown hysterical tendencies. He had spells of blindness, deafness, and aphonia when he wished to dodge unpleasant duties. These tendencies were all more marked and troublesome as sequelae of his attack of encephalitis.

Tics.—Irregular movements of the head or of one extremity, sniffing of the nose, clicking of the tongue, biting the finger nails and obsessive spitting have been observed in these cases. These tics are considered to be of organic origin following encephalitis.

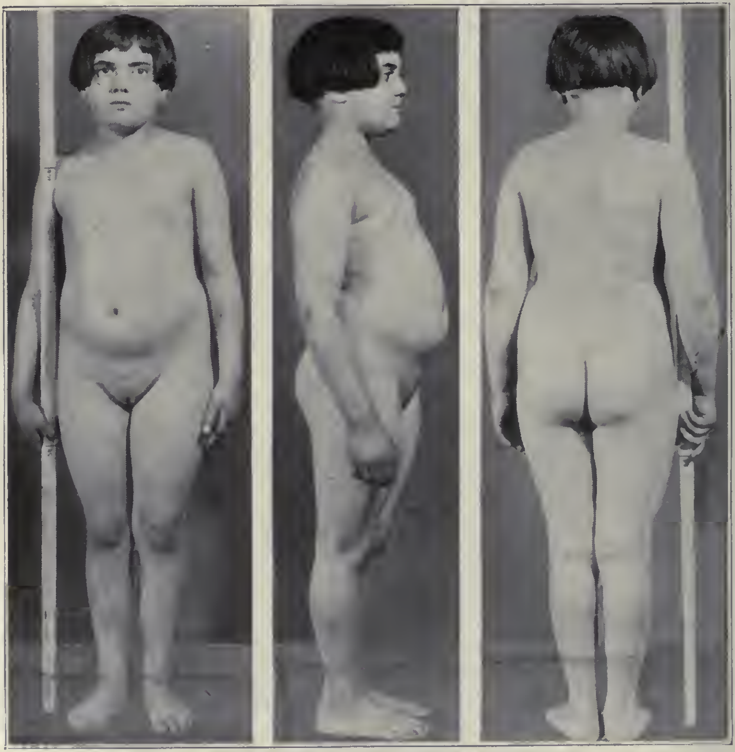


Fig. 1 (Case 2).—Anterior, lateral and posterior views of patient that had suffered an attack of encephalitis in February, 1919, which was followed by evidence of endocrine disturbance of a hypopituitary type. The illustrations show the distribution of the fat. Laboratory reports revealed increased sugar tolerance; basal metabolism, 16 per cent. above normal. The sella turcica was normal.

Mental Deficiency.[9]—We have found mental deficiency to be one of the sequelae especially to be considered, if encephalitis occurs during infancy. Cases 3, 16 and 17 belong in this class. Two of these patients developed the disease at the age of 2 years. One of the two is now 6 years of age, but her mental age, determined by the routine psychologic examination, remains 2 years. Previous to her acute illness she showed normal mental development. One infant evidently had encephalitis at birth. Two years later she presented the picture of an idiot. The evidence in this case, as in the cases reported by Jorge and Mercier,[10] suggests that congenital encephalitis occurs.

---

[9] Paterson, D., and Spence, J. C.: The After-Effects of Epidemic Encephalitis in Children, Lancet **2**:491 (Sept. 3) 1921.

NEUROLOGIC SEQUELAE

The neurologic sequelae can briefly be referred to as, first, subjective complaints, and secondly, objective manifestations. Headaches, dizziness, diplopia, drowsiness during the daytime, and asthenia constitute the main subjective symptoms. Oversalivation also was present and was a troublesome factor in a large percentage of our cases.

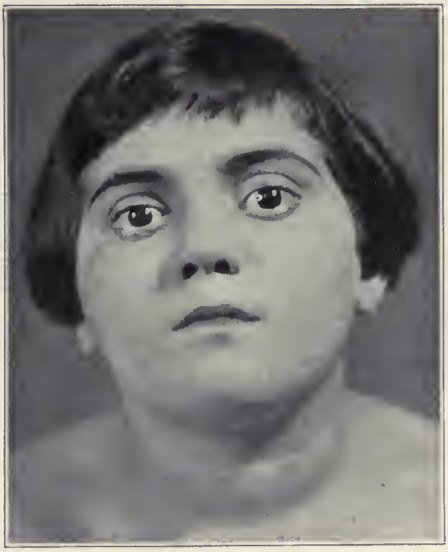


Fig. 2 (Case 2).—Appearance of patient, showing tendency to exophthalmos which may indicate thyroid activity to compensate for hypopituitarism; also showing residual left-sided ptosis.

Disturbance of Motility.—This was a very common finding. It consisted of choreiform and all types of incoordinated movements which occurred for prolonged periods in seven cases (Cases 1, 2, 3, 9, 12, 14 and 16). It is interesting to note that these disturbances in motility were apparently related to the behavior and emotional changes mentioned above. I say this because emotional stimuli brought on the irregular, incoordinated movements. These movements frequently occurred during sleep and were not for the most part accompanied by pain. Radiculitis of a severe type was present in only one case, and in this child we found also choreo-athetoid movements. Tremors were frequent, though not especially characteristic.

---

[10] Jorge, R.: Epidemic Encephalitis and Pregnancy. Transmission of the Disease by the Mother to the Fetus, Paris méd. **2**:454, 1921. Mercier, R.: Placental Transmission of Epidemic Encephalitis, Bull. de l'acad. de méd. **85**:625 (May 31) 1921.

Visual Disturbance.—Weakness or paralysis of one rectus muscle was observed in seven cases (Cases 1, 2, 5, 6, 12, 14 and 16). The sixth nerve was the one most frequently affected. Ptosis of a marked degree was not present. It was noted in two cases as a permanent finding (Cases 2 and 14). Eye ground examinations were negative with one exception in which there was a mild degree of optic neuroretinitis present for a short period. Many children complained of difficulty in reading. The visual defects of some improved after appropriate lenses were fitted.

Other Neurologic Findings.—Facial weakness was observed in only two cases. Evidence of pyramidal and extrapyramidal tract involvement was noted in one child. Involvement of the corpus striatum was considered to be present in this case which accounted for a rigidity of one side of the body and immobile facies. No other patient in this series showed any evidence of a paralysis agitans syndrome.

Disturbances of the autonomic system consisting of oversalivation, and vasomotor symptoms were present. Exophthalmos developed in one child as a sequela of the disease.

Endocrine Findings.—One case showed the characteristic findings of hypopituitarism, and obesity was a development in several patients (Figs. 1 and 2). States of undernutrition have also occurred.

PROGNOSIS

The prognosis of acute epidemic encephalitis in children should be made very conservatively. I do not wish, however, to give a pessimistic outlook. In this series of seventeen patients, five (Cases 1, 11, 13, 14 and 15) have been progressively improving, and eventual recovery without a permanent residual pathologic condition is expected. Four others are improving slowly (Cases 5, 6, 7 and 9), although the ultimate outlook remains doubtful. The remaining eight children seem to be unimproved, three of them appearing to be permanently mentally deficient. Improvement, therefore, and possibly complete adjustment are to be expected in approximately half of these cases. A period of five years should be allowed to determine the permanency of the neuropsychiatric sequelae.

TREATMENT

There is no specific treatment for encephalitis. Medicine, as is usual in organic cases, has been of no avail. Routine sedatives and hypnotics have not produced sleep. Continuous warm baths have been of use in some cases during periods of excitement. Spinal drainage has given conflicting results. In four cases, however, there appeared to be transient improvement following this procedure. One child apparently was made worse. Psychotherapy has been disappointing in this application. Occupational therapy has proved to be of value. A prolonged period of observation and treatment in the hospital ward appears advisable, especially since this creates a new environment for the patient, which may be helpful. This constitutes one of the aspects of the universal need for a children's psychopathic ward. In a few cases, commitment may be indicated. These patients did not react well to discipline. However, a well regulated home routine and discipline were advised, especially for patients showing hysterical tendencies.

SUMMARY

In the seventeen cases of postencephalitis disturbances of a neuropsychiatric type the psychiatric sequelae consisted of: (1) total change in character and disposition with characteristic hyperkinetic states, leading to behavior oddities consisting of emotional lability, sexual precocity, general incorrigibility, etc.; (2) insomnia with nocturnal agitation; (3) affective disorder of a depressive type; (4) hysterical reactions; (5) tics, fears, and (6) mental deficiency.

Neurologic sequelae consisted of headaches, dizziness, diplopia, drowsiness, asthenia and oversalivation. Disturbances in motility, especially choreiform movements, were present. These disturbances appear to be related to the mental state. Visual disturbance and facial weakness also occurred as residuals. Evidence of endocrine change was noted in one case.

The prognosis should be guarded; but pessimism should be avoided. Fifty per cent. of these patients are well or improving.

There is no specific treatment for these conditions. Children should be sent to psychopathic wards for observation. Spinal drainage was effectual in several cases. These children do not react to discipline.

ACUTE HEMORRHAGIC ENCEPHALITIS

REPORT OF A CASE FOLLOWING SCARLET FEVER *

JOHN A. TOOMEY, M.D.; LEON H. DEMBO, M.D.,
AND
GUTHRIE McCONNELL, M.D.
CLEVELAND

The comparative infrequency of acute hemorrhagic encephalitis as a sequela of scarlet fever, the clinical picture presented, and the unusually rapid course of the case here recorded, with fatal termination, are points of sufficient interest to justify a rather detailed report.

REPORT OF CASE

History.—E. G., boy, white, aged 6 years, was admitted, July 31, 1922, suffering from convulsions. The mother stated that until three days previously he had apparently been in good health since he had had scarlet fever. He had been active in play, and had made no complaint. July 28 he complained of sore eyes, avoided light, and had some apparent stiffness of the right leg. A physician was summoned, and, following treatment, there was some improvement. The next day he vomited everything taken by mouth, was feverish, and the mother noted that he seemed drowsy and had a squint. At this time there was rigidity of the right leg. He was much worse on the following day, the lethargy increasing and the vomiting becoming more marked. He could, however, be aroused. That evening he began to have convulsions which started with twitching of the fingers and finally became generalized. A lumbar puncture was done by the physician in attendance, and bloody fluid was withdrawn, which was attributed to faulty technic. The convulsions persisted, and there was involuntary evacuation of the bowels and bladder. The boy was placed in hot packs, but the convulsions continued, lasting from one half to one hour. The patient rapidly lapsed into coma and was sent to the contagious division of the City Hospital, July 31, at 11 a. m.

The father and mother of the boy were living and well. One brother, aged 11, was living and well. The mother had never had any miscarriages, and there was no history of cancer or tuberculosis in the family.

The child had measles at 7 months, chickenpox at 4 years, and he had had frequent attacks of sore throat, especially during the winter months. He had been breast fed until the age of 11 months. Congenital clubbed feet were corrected during the first two years. He had always been a robust child and had never had any serious illness. July 7 the mother noticed that he seemed to have some fever. He was put to bed, and a physician, who was called, stated that the child looked as if he were going to have an attack of one of the acute exanthems. The next day a typical scarlatiniform rash appeared. The child remained in bed for the following three days and was then allowed to be up without the permission of the attending physician. He seemed to be getting along fairly well, and during the next three weeks played as usual. July 28 the present illness began with the complaint of sore eyes and drowsiness.

Physical Examination.—On admission he was comatose, and was having frequent convulsions. He was well developed and well nourished. Cyanosis was well

---

* Received for publication Dec. 12, 1922.

* From the Departments of Pathology and Pediatrics, Western Reserve University, and the Division of Contagious Diseases, City Hospital.

marked, and respirations were of the Cheyne-Stokes type. There was marked rigidity of the arms and legs. The head presented no abnormalities. The eyes were fixed and staring, and the pupils were contracted to almost pin points and not reacting. The ears and nose were negative. The lips were cyanotic, the mouth was open, and the tongue protruded slightly; the teeth were negative. There was some rigidity of the neck. The thorax was well developed, symmetrical and presented no bony abnormalities. The respirations were shallow. Moist râles were heard throughout the chest. Percussion revealed nothing remarkable. The heart beats were rapid and regular; the sounds were heard well and were of good muscular quality. There were no murmurs, and there was no apparent enlargement. The abdomen was well rounded, somewhat rigid, but moving with respiration. No masses were palpable. The extremities were cyanotic, especially the legs. The skin was hot, dry and cyanotic. The temperature on admission was 40.4 C. The pulse was rapid, bounding and of alternating volume.

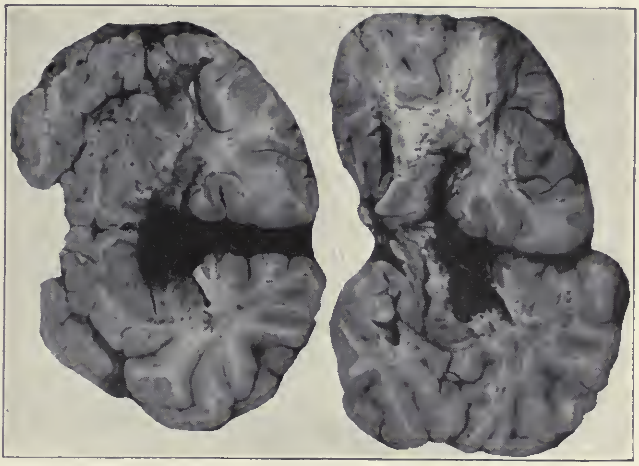


Fig. 1.—Transverse section through midbrain showing hemorrhage of the ventricular floor.

Diagnosis.—From the past history of scarlet fever and the character of the onset of the present illness, a diagnosis of nephritis with uremia was made. Because of the serious condition of the child a detailed examination could not be made.

Treatment.—The boy was immediately placed in a hot pack and given stimulation by the hypodermic route. Rectal injections of chloral and bromids were given to control the convulsions. When he was being removed from the pack, respirations ceased, and, in spite of artificial respiration and circulatory stimulation, death ensued. The entire course from the time of admission to death was not more than forty-five minutes in duration.

Necropsy Report.—The body is that of a well developed, well nourished white male child, aged 6 years.

Head: There are no abnormalities of the scalp, calvarium or meninges. The brain weighs 1,430 gm. and presents no abnormalities of the external surface.

The ventricles are full of blood and clots. The basal nuclei are hemorrhagic, soft and friable, and, where they are of such consistency that they can still be cut, are filled with many petechiae. Serial section of the brain reveals the more marked destruction of the thalamus on the left side than on the right. The superficial portions are necrotic and hemorrhagic. Beneath this area there is a zone of pinpoint hemorrhages. On the right side the hemorrhage has taken place in the subependymal tissues.

Peritoneal Cavity: The peritoneum is smooth and glistening. There are no adhesions present and no fluid. The appendix is retrocecal and bound down by adhesions. The thoracic viscera show no gross abnormalities. The pericardial cavity shows a smooth and glistening lining, with no excess of fluid. The mucosa is pale and of normal thickness. The endocardium is smooth and glistening throughout, except for several pinpoint to pinhead petechiae found in the left ventricle. The valves are entirely normal.

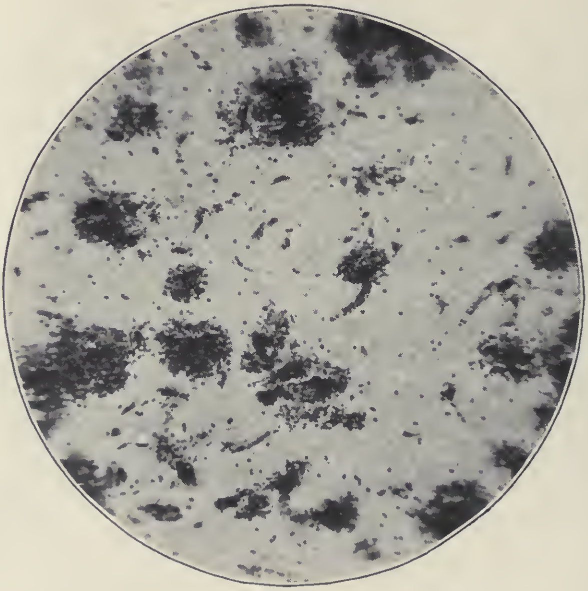


Fig. 2.—Section showing multiple hemorrhages in the brain tissue.

Lungs: The external surfaces are smooth, shiny and bright red. Crepitation is present throughout. On section the tissue is bright red. There is no excess of fluid and no consolidation. The bronchi are slightly congested. The aorta is smooth, glistening and elastic throughout. The spleen is enlarged and the capsule smooth. It is a pale brick red, and on section it is a pale, bluish red, the malpighian bodies and trabeculae being normally prominent. The organ is not friable. The suprarenals show no gross abnormalities.

Kidneys: The capsules strip with ease. The surfaces are smooth, and, on section, they do not bulge. The cortices are regular and the striations well marked. The right kidney is congested, the pyramids being of a purplish color. The left kidney is pale. There are no abnormalities of the pelves of the ureters.

Liver: The liver is normal in shape and consistency. The capsule is smooth and a brownish red with yellow mottling. The architecture is well preserved. The gallbladder contains a small amount of dark, viscid bile. There are no gross abnormalities.

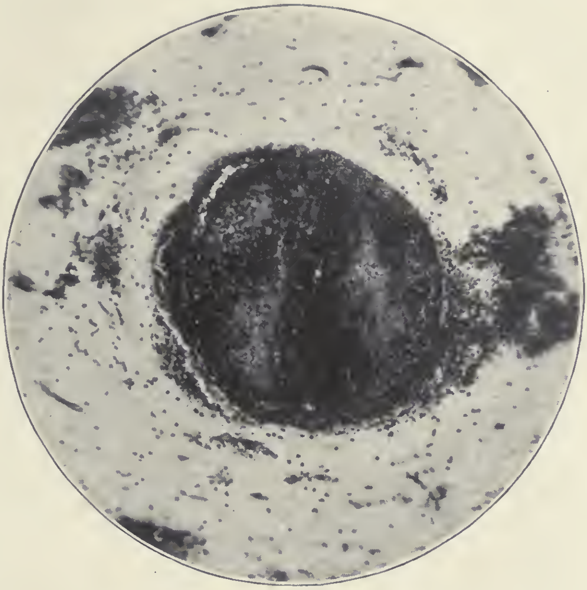


Fig. 3.—Section showing thrombosis of cerebral vessels.

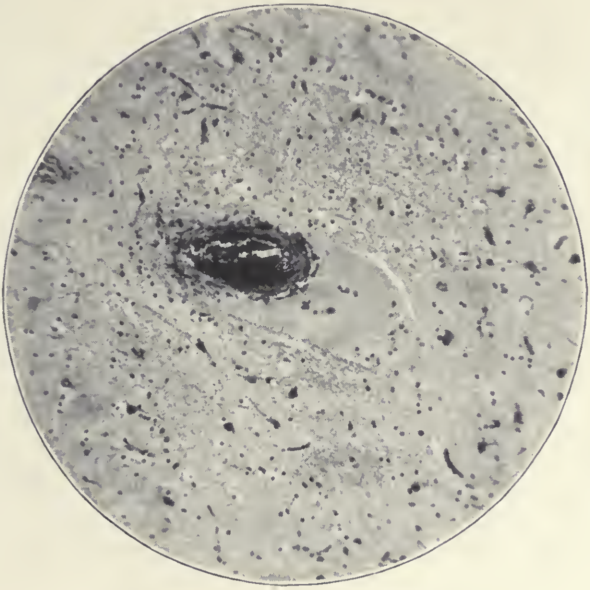


Fig. 4.—Section showing congestion with exudation in the perivascular lymph spaces.

Stomach: The stomach contains a small amount of digested food. The mucosa is smooth and white. The duodenum, pancreas, small and large intestines, bladder and prostate are normal. The thymus is about the size of a hickory nut and is soft and vascular.

Anatomic Diagnosis.—Edema of the brain; acute hemorrhagic softening of the basal nuclei, with intraventricular hemorrhages; subendocardial petechiae (left ventricle); congestion of the spleen.

Microscopic Examination.—Heart: There is slight cloudy swelling and vacuolation of muscle fibers. Section of the wall of the left ventricle shows an extensive subendocardial hemorrhage surrounding, and in some instances destroying, the Purkinje cells.

Lungs: Many abnormally large alveoli resulting from the rupture of the alveolar walls are present. There is diffuse congestion and infiltration of the peribronchial tissues by many lymphocytes, with some desquamation of the bronchial epithelium.

Liver: Lobulation is unusually distinct. The portal tissue is well developed, and the liver cells at the periphery of the lobule contain an abnormal amount of a granular, brownish pigment. Sinusoids contain more leukocytes and lymphocytes than is usual. There is some periportal leukocytic infiltration.

Spleen: There is endothelial hyperplasia, but no congestion. The leukocytes are greatly increased in number. The germinal centers are quite distinct.

Pancreas: In a few of the lobules are areas in which the acini are apparently atrophic and the amount of fibrous tissue increased. The suprarenals and the thymus show nothing abnormal.

Brain: Many of the blood vessels are completely occluded by thrombi of recent formation. There is no evidence of cellular proliferation. The walls show degenerative changes and are outlined by deeply staining fragments of broken down nuclei. Many of these thrombosed areas are surrounded by distinct zones of hemorrhage. There are also many apparently isolated areas of hemorrhagic infiltration, varying greatly in extent. In many instances the perivascular lymph spaces are greatly distended by a coagulated exudate. The brain tissue adjacent to these areas is edematous. A few leukocytes are scattered here and there, but no definite leukocytic infiltration is present.

SUMMARY: Thrombosis of cerebral vessels accompanied by edema and hemorrhagic infiltration; pulmonary emphysema; pigmentation of liver; endothelial hyperplasia of the spleen.

COMMENT

A search through the literature reveals some interesting case reports similar to this one in symptomatology, but differing in that many of the patients partially recovered, retaining some degree of paralysis. By far the majority of cases occurred as late sequelae of influenza, although many followed in the wake of other acute infections. Putnam[1] reports a case occurring in a boy, aged 13, following an attack of mumps. The chief symptoms in this case were headache, drowsiness, delirium, numbness of the extremities, a partial ptosis of the eyelids with an internal strabismus of the right eye. These symptoms were followed by deafness, optic neuritis and bulbar symptoms. Oppenheim[2] reports several cases of long duration with partial recovery. In one case, that of a girl, aged 16, the duration was four months, the main symptoms being headache, motor and sensory aphasia, and optic neuritis. In this case the outcome was favorable. Another patient, a girl, aged 10, was stricken three months after a slight attack of influenza. Fever, loss of speech, optic neuritis, prostration, stiffness of the neck muscles and unconsciousness lasting three days characterized the clinical picture in this case. The final outcome in this case was also favorable. Nauwerck's [3] case occurred in a girl, aged 14, during an epidemic of influenza. Remittent fever, convulsions limited to the left side, vomiting, coma and death comprised the notable clinical features. Necropsy revealed the brain to be soft and edematous, with numerous foci of hemorrhagic softening. Fürbringer [4] cites a case following scarlet fever, occurring in the fifth week after the primary illness. Königsdorf [5] and Schmidt [6] described rather typical cases occurring during the epidemic of influenza in 1889-1891. In the latter's case, the patient, a girl, aged 19, was suffering from chlorosis. The clinical picture was characterized by headache, apathy, epileptic seizures and somnolence. Later the breathing became stertorous, the pupils were small and failed to react to light, and there was conjugate deviation. Necropsy revealed hemorrhagic encephalitis, with blood in both lateral ventricles, especially in the left ventricle.

---

[1] Putnam, J. J.: J. Nerv. & Ment. Dis. **24**: (Jan.) 1897.

[2] Oppenheim, N.; Die Prognose der akuten, nicht-eitrigen Encephalitis, Deutsch. Ztschr. f. Nervenh. **6**:377, 1894.

Etiology.—Several theories have been advanced as to the causative factors, chief of which are the bacterial and the toxic. The former supports the hypothesis that this type of encephalitis is due to a direct invasion of the cortex of the brain (Hoppe [7]) by the bacteria which cause the primary disease; the latter attributes the cause to a toxic product of the acute infectious diseases.

Regarding sex, male and female are equally affected. Relative to age, the period of greatest frequency ranges from early childhood to puberty.

Hoppe [7] states that measles is frequently complicated with encephalitis; next in order are typhoid, scarlatina and diphtheria. A characteristic feature of this complication is that it usually occurs during the period of convalescence, or, not infrequently, weeks or months later.

---

3. Nauwerck: Influenza und Encephalitis, Deutsch med. Wchnschr. **21**:393, 1895.

4. Fürbringer, P.: Deutsch med. Wchnschr., 1892, No. 3.

5. Königsdorf: Ein neuer Fall von akuter haemorrhagischer Encephalitis, Deutsch med. Wchnschr. **18**:182, 1892.

6. Schmidt, J.: Akute primäre hemorrhagische Encephalitis, Deutsch. med. Wchnschr. **18**:703, 1892.

7. Hoppe, N. M., in Tice's Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc. **9,** 1920.

Of the cases occurring in adults influenza is the cause in the vast majority. Freyhan[8] states that the main feature is found in the small hemorrhages which come from the dilated and overfilled capillaries.

Trauma is mentioned as a factor. Drinkler[9] described a case occurring in a young child, who, following a severe blow on the head two and a half years before, had developed symptoms characteristic of hemorrhagic encephalitis. Hoppe's[10] case occurred in a boy, following a fall. At necropsy, the brain was seen to contain many hemorrhagic cysts. The influence of trauma may be brought about in a purely mechanical way, combining the factors of concussion and inflammatory reaction followed by softening. Again, a secondary circulatory infection may intervene, causing a localized or circumscribed inflammatory process.

Pathology.—There are two distinct types of acute hemorrhagic encephalitis which differ clinically and pathologically. Under the term "acute hemorrhagic encephalitis" is included the so-called "Strümpell-Leichtenstern" form. This type was first described by Strümpell in his paper on infantile cerebral palsies. The second is the syndrome characterized by multiple hemorrhages occurring most frequently in the cortex, less commonly in the basal ganglions.

The color varies according to whether the hemorrhages are recent or late, the pigment changes being from a purplish brown to a brownish yellow tint. There is dilatation of the arterioles and capillaries and a transudation of red and white blood corpuscles into the surrounding tissue. The ganglionic cells are secondarily affected, the protoplasm undergoing swelling and the nuclei becoming less distinct. In those cases in which the hemorrhagic areas are extensive, involving a large cortical area, the basal nuclei and the walls and floor of the ventricles, the outcome is invariably fatal. In those cases, however, which are less extensive and terminate in recovery, the patient is left with cortical defects resulting from fibrotic changes with the formation of scar tissue. Strümpell's contention was that these scars were the cause of the palsies seen in childhood following an attack of this type of encephalitis.

Occasionally there is cyst formation. Oppenheim stated that this form of encephalitis was frequently associated with sinus thrombosis and thrombosis of the veins in cases in which there was, clinically, a well marked chlorosis.

---

[8] Freyhan: Ueber Encephalitis hemorrhagica, Deutsch. med. Wchnschr. **21**:643, 1895.

[9] Drinkler, M.: Mitteilung eines tödlich verlaufenen Falles von traumatischer Gehirnerkrankung (allgemeine Unruhe, Schwachsinn, Sprachstörungen, u.s.w.) mit dem anatomischen Befunde einer Polioencephalitis hemorrhagica inferior acuta, Deutsch. Ztschr. f. Nervenh. **6**:465, 1895.

[10] Hoppe, H. H.: J. Nerv. & Ment. Dis. **29**:9, 1902.

In Wernicke's syndrome the lesion involves the gray nucleus of the third nerve and the gray matter of the thalamus, with some capillary hemorrhages in the cortex. The essential pathologic processes consist of vascular changes, with hemorrhage and destruction of the gray matter.

Symptomatology.—The clinical manifestations of the Strümpell-Leichtenstern type are many and varied, and, except for those observers who have seen and dealt with a great number of these cases, present no distinctive features. Occurring during an epidemic in which many such cases are prevalent, the symptoms might at once suggest the true condition. In isolated instances, however, as in the case here reported, a clinical diagnosis could hardly be made with certainty, especially since the picture presented a syndrome that might well have been mistaken for uremia.

The onset is usually some time after recovery from one of the acute infectious diseases. There may be some distinct prodromal symptoms, such as headache and malaise. More often the onset is sudden, with headache, fever, restlessness, convulsions, rigidity of the extremities, and a rapidly developing coma. Ocular symptoms are common and are manifested by ptosis, strabismus and inequality of the pupils, with failure to react to light. The respirations are of the Cheyne-Stokes type. In cases terminating in death, the coma increases, and respiratory failure (as in our case) occurs.

The Wernicke type is characterized by marked delirium, paralysis of the external eye muscles, ptosis, strabismus, facial paralysis, constipation, and, not infrequently, vomiting.

Course and Duration.—The course and duration vary, depending on the extent of involvement. In those cases in which the hemorrhagic areas are confined chiefly to the cortex, the disease may run a course of from several days to many weeks, terminating in partial recovery. In fulminating cases, in which the cortex, basal nuclei and walls and floor of the ventricles are involved, death may follow within from twenty-four to forty-eight hours after the onset.

Diagnosis.—A number of conditions must be considered. Cerebral abscess, uremic focal symptoms, thrombosis, and cerebrospinal meningitis are the important conditions entering into the question of diagnosis. The case of Norris [11] illustrates some of the difficulties encountered in the diagnosis of this condition. His patient, a man, aged 28, after returning from the day's work, was found unconscious. There were twitching of the side of the face, a partial paralysis of the right arm and leg, and slight nystagmus. Lumbar puncture revealed a cell count of 1,250, with the fluid under increased pressure. The eyegrounds were negative. There was a paralysis of the right side without spasticity. Positive Babinski and Oppenheim reactions were present, with moderate cervical rigidity. He had been in the hospital three weeks prior to his present admission, suffering from a bilateral lobar pneumonia. On the strength of this history, together with the suggestive physical findings, a diagnosis of meningitis was made, probably pneumococcic. Necropsy revealed the true nature of the condition—an acute hemorrhagic encephalitis.

---

[11] Norris, G. W.: Acute Hemorrhagic Encephalitis, Internat. Clin. **1**:24-28, 1922.

As stated, when this disease appears as the aftermath of an acute infection, in the absence of an epidemic, the diagnosis is extremely difficult. It is unfortunate that in our case we were unable to make a more thorough examination. The few hurried observations made were scarcely sufficient to present even a clue to the underlying condition.

Treatment.—The treatment is largely symptomatic. The prognosis is at best unfavorable. In some cases in which partial recovery occurs, there is usually some defect either in the form of epileptiform seizures, an obtunded mentality, or some degree of paralysis. Many question the diagnosis in cases in which recoveries are reported.

SUMMARY

1. The fatal case of acute hemorrhagic encephalitis reported was a late sequela of scarlet fever.
2. The hemorrhages found in the brain and the character of the onset and symptoms conform to the description of the Strümpell-Leichtenstern type.
3. The diagnosis is difficult because of the resemblance of this disease to other more common diseases.
4. The prognosis is unfavorable in the majority of cases.

INTRAPERITONEAL TRANSFUSION WITH CITRATED BLOOD

AN EXPERIMENTAL STUDY *

DAVID M. SIPERSTEIN, M.A., M.D.
Fellow in Pediatrics, University of Minnesota
MINNEAPOLIS
AND
J. MARTIN SANSBY, B.S., M.D.
ST. PAUL

Blood transfusion in infants and children is a recognized therapeutic procedure. In the past, the site of transfusion has been limited to the superior longitudinal sinus in the region of the anterior fontanel, or to the direct exposure of some vein, preferably in the elbow.

The anterior fontanel route, popularized by Helmholz[1] in 1915, affords an excellent method in infants in whom this structure is accessible. This approach, however, has its limitations. Fischer,[2] Lowenburg,[3] Unger,[4] and others, have pointed out the dangers inherent in puncturing the superior longitudinal sinus.

In older infants, those more than 18 months of age, the fontanel is not usually patent, and the only other procedure remaining is the exposure of a vein and the injection of the donor's blood. We need not go into a discussion concerning the technical considerations involved in this method. It is conceded that the number of blood transfusions in young children has been influenced markedly by the difficulties encountered.

In view of these existing dangers and limitations, it was thought that another avenue of approach which would be safe, simple to apply, and which would afford fairly rapid results, would be of value. It is the purpose of this paper to outline a method which meets these fundamental requirements.

PROBLEM

The intraperitoneal transfusion of citrated blood offers a feasible and practical solution of this problem. In order to demonstrate the

---

* Received for publication, Nov. 6, 1922.

* From the Department of Pharmacology, University of Minnesota.

[1] Helmholz, H. F.: The Longitudinal Sinus as the Place of Preference in Infancy for Intravenous Aspirations and Injections, Including Transfusion, Am. J. Dis. Child. **10**:194 (Sept.) 1915 .

[2] Fischer, L.: The Superior Longitudinal Sinus in Infants; Its Value in Transfusion and for Rapid Medication, Med. Rec. **94**:399 (Sept. 7) 1918.

[3] Lowenburg, H.: Blood Transfusion via Longitudinal Sinus, with Report of Cases, Therap. Gaz. **44**:381 (June 15) 1920.

[4] Unger, L. J.: Transfusion of Unmodified Blood, J. A. M. A. **69**:2159 (Dec. 29) 1917.

utility of this proposed method it is necessary to show: (1) that the red blood cells are absorbed from the peritoneal cavity; (2) that they reenter the blood stream as red blood cells, and (3) that they are capable of functioning after reentering the general circulation.

REVIEW OF LITERATURE

ANIMAL EXPERIMENTS SHOWING ABSORPTION FROM THE PERITONEAL CAVITY

In 1862, von Recklinghausen[5] injected defibrinated blood into the peritoneal cavity of rabbits and found that absorption took place.

Ponfick,[6] in 1875, noticed an increase in red blood cells which reached a maximum in one or two days following the intraperitoneal injection of defibrinated blood.

Bizzozero and Golgi,[7] also working on rabbits, in 1880, reported an increase in hemoglobin following the intraperitoneal injection of defibrinated blood. They were able to note a change in twenty minutes which increased gradually up to the first or second day and persisted for about a week. They found that in anemic rabbits the hemoglobin increased more rapidly, and persisted for a long time (in one case twenty-seven days).

Poncet[8] in 1879, while studying periuterine hematocele experimentally, noticed the constant complete disappearance of the blood injected into the peritoneal cavity.

Arloing and Tripier[9] verified these experiments by connecting the carotid of one animal directly with the peritoneal cavity of another. They found that rapid absorption invariably took place.

In 1880, Obalinski[10] found an increase in red blood cells one hour after the injection of defibrinated blood which persisted for a long time. The greatest increase was 49 per cent., the lowest 12 per cent., independent of the amount of blood injected. He was unable to demonstrate a hemoglobinuria at any time.

During the same year, Foa and Pellacani[11] showed that peritoneal transfusion of blood in dogs led first to a hyperplasia, and later to a true functioning of the bone marrow. They thought that the increase in hemoglobin due to the transfusion itself lasted only a few days.

Maas,[12] in 1881, injected small amounts of defibrinated blood into the peritoneal cavity of dogs and rabbits—after producing a secondary anemia. Blood counts taken five hours later showed an increase of from ½ to 2½ million cells per c.mm. The blood count gradually fell to normal. The increase in red blood cells varied directly with the amount injected.

---

5. Von Recklinghausen, F. V.: Zur Fettresorption, Virchows Arch. f. path. Anat. **26**:172, 1863.

6. Ponfick: Experimentelle Beiträge zur Lehre von der Transfusion, Virchows Arch. f. path. Anat. **62**:273 (Jan. 20) 1875; also Berl. klin. Wchnschr. **16**:589 (Sept. 29) 1879.

7. Bizzozero, G., and Golgi, C.: Della trasfusione di sangue nel peritoneo e della sua influenza sulla ricchezza globulare del sangue circolante, Arch. per. le sc. med., Torino **4**:67, 1880.

8. Poncet, quoted by Lesage: De l'hematocèle periuterine, These d'agregation, 1878.

9. Arloing and Tripier, quoted by Lesage: Recueil d. méd. vét. **7**:350 (June 15) 1900.

10. Obalinski, A.: Experimenteller Beitrag zur peritonealen Bluttransfusion, Przegl., lek. No. 9 i. 10 Polmsile; abstr. Jahresb. f. med. Wissensch., 1880, p. 314.

11. Foa, Pio, and Pellacani, Paolo: Ricerche sperimentali sulla trasfusione del sangue e sugli effetti delle scottature, Ann. med. **251**:478, 1880; abstr. Jahresb. d. ges. Med. **15**:312, 1880.

12. Maas, G.: Ueber intraperitoneale Bluttransfusion bei Thieren, Königsberg, Hartung, 1881.

In 1884, Hayem[13] reported an extensive and ingenious set of experiments, using rabbits and dogs. He obtained rapid and complete absorption of blood —whether defibrinated or not. He was never able to find any change in the morphologic structure of the red blood cells which were unabsorbed at the time necropsy was performed. He noticed that in case of autotransfusion, only a transitory anemia resulted. In cases in which an anemia was produced and an equivalent amount of blood injected, only a transitory anemia was apparent. On transfusing a normal animal, a plethora resulted. In order to prove definitely that the cells were absorbed as such, he hit on the idea of injecting rabbit's blood into the peritoneal cavity of a dog, with the intention of demonstrating the much smaller erythrocytes of the rabbit in the general circulation of the dog. However, he found that dog's blood contained hemolysins for the red blood cells of rabbits and he was able to show hemoglobin in the dog's serum. On trying the inverse experiment, on the other hand, he found the cells of the dog in the general circulation of the rabbit. He came to the conclusion that a peritoneal transfusion was equivalent to a very slow intravenous transfusion.

Marcus,[14] in a later publication, confirmed Hayem's results.

Ledderhose,[15] in 1885, demonstrated an increase in hemoglobin following the injection of blood into the peritoneal cavity of dogs.

William Hunter,[16] 1886-1887, working on rabbits, found that from 32 to 92 per cent. of the total amount of an animal's own blood could be injected intraperitoneally without ill effects. He got a slight rise in blood count with a subsequent fall on the second day, then a more permanent rise, reaching its maximum on the fifth or sixth day and persisting for about twenty-six days. He obtained similar results with defibrinated blood, but noted that the corpuscles were destroyed somewhat more rapidly than when using whole blood. He advised against this method as a therapeutic measure, chiefly because of the danger of peritonitis, and because only a relatively small amount of blood could be introduced at one time, and this, in turn, he thought, was rapidly destroyed.

In 1898, Southgate,[17] was able to transfuse an animal with the blood from another animal of the same species, and obtained an increase in red blood cells of 10, 11 and 4 per cent. at the end of the first, second and third hours, respectively. There was no hemoglobinuria. From further rather meager experimental data he drew the following conclusions:

> 1. Direct transfusion of arterial blood from one animal to the peritoneal cavity of another animal of the same species causes no perceptible injury to the animal receiving the blood.
> 2. Homogenous, nondefibrinated blood is quickly reabsorbed from the peritoneal cavity.
> 3. Homogenous blood reabsorbed from the abdominal cavity does not produce hemoglobinuria, but seems to be absorbed and to circulate as normal blood.
> 4. After hemorrhage, if there be sufficient compensation by transfusion into the peritoneal cavity, the general circulation changes very little or not at all.
> 5. Simple intraperitoneal transfusion of blood enriches the blood of the animal receiving it and the increase in corpuscular elements reaches its maximum in three hours.
> 6. Transfusion of foreign or heterogeneous blood into the abdominal cavity of rabbits produces hemoglobinuria and results in the death of the animal.

Vogel[18] opened the abdominal cavity of a rabbit, allowed a quantity of blood to flow into it from an artery and then closed the incision. At necropsy, seven days later, he found no blood or adhesions.

---

[13] Hayem, M. G.: De la transfusion péritonéale, Compt. rend. **98**:748 (Jan.-June) 1884.

[14] Marcus, S. H.: Die peritoneale Transfusion, Wien. med. Presse **25**:492, 1884.

[15] Ledderhose: Beiträge zur Kenntniss des Verhaltens von Blutergüssen in serösen Höhlen unter besonderer Berücksichtigung der peritonealen Bluttransfusion, Strasbourg, 1885.

[16] Hunter, William: Intraperitoneal Blood Transfusion and the Fate of the Absorbed Blood, J. Anat. & Physiol. **21**:138, 264, 450, 1886.

[17] Southgate, F. H.: Ueber Blutresorption aus der Peritonealhöhle, Centralbl. f. Physiol. **8**:449, 1894; Blood Absorption from the Peritoneal Cavity, Med. Rec. **48**:221 (Aug. 17) 1895.

[18] Vogel: Klinische und experimentelle Beiträge zur Frage der peritonealen Adhäsionen nach Laparatomien, Deutsch. Ztschr. f. Chir. **63**:363.

Lesage,[19] in 1900, reported his results in a series of experiments, using dogs and oxen. He found that, in dogs, absorption of blood following autotransfusion was complete in forty-eight hours, and that, at that time, the peritoneal cavity was absolutely normal in appearance. In a series of twenty-one animals, ranging in weight from 4 to 20 kilograms, transfused with from 75 to 200 c.c. of whole blood, and on whom the necropsy was made from forty-five minutes to forty-eight hours after the transfusion, there was complete absorption in three instances at the end of forty-eight hours. He found clots in the peritoneal cavity in nearly all his animals. In three other animals, receiving blood from another animal of the same species, absorption was complete in one instance at the end of forty-eight hours. In a later publication during the same year, he was able, by a very skilful method, to show the absorption of blood from the abdominal cavity. After an autotransfusion of 200 c.c. of blood obtained from the carotid and injected into the peritoneal cavity, he made a fistula of the thoracic duct. Forty-five minutes later the normally colorless, slightly opalescent lymph coming from the duct became rosy. The color gradually became more pronounced so that one hour after the operation it had a definite red tinge. Microscopic examination revealed large numbers of free red blood cells absolutely normal in appearance. No phagocytosis was demonstrable. However, at the necropsy, made forty-eight hours later, he found mononuclears gorged with red blood cells. He concluded that an hour after transfusion, red blood cells commence to pass freely without change into the thoracic duct. Then after the active diapedesis at the level of the peritoneum, the leukocytes come out and engulf the tardy red blood cells and go with them into the lymphatic circulation, the serosa returning to its normal aspect several days after the transfusion.

Skutsch,[20] in 1906, placed relatively large amounts of blood in the peritoneal cavity of rabbits and found complete absorption twenty-four hours later. He was unable to demonstrate any evidence of peritonitis, clots or adhesions.

In 1906, Buxton and Torrey,[21] in an extensive and thorough research, were able to show that after the injection of various foreign particles (lampblack, typhoid bacilli, hen's red blood cells, etc.) into the peritoneal cavity of guinea-pigs, there was an immediate rush of these particles to the lymphatics of the diaphragm. From there they passed along the anterior mediastinal lymph trunks, through the nodes, into the thoracic duct and finally into the blood stream. This took place very rapidly and the particles were practically in a free state. Phagocytosis was seen later, chiefly in the anterior mediastinal nodes.

In 1921, Zimmermann[22] was able to show that absorption of whole blood took place very rapidly from the abdominal cavity. Working on rabbits and guinea-pigs, he found that absorption was complete in forty-eight hours. There was no evidence of peritonitis at any time. He injected bird's blood into rabbits and guinea-pigs. He demonstrated the cells of the bird in the guinea-pig's circulation in five minutes. In the rabbits, nucleated cells were found from fifteen to thirty minutes after the injection. He found these cells in the thoracic duct and lymph nodes in large numbers.

CLINICAL EXPERIMENTS SHOWING ABSORPTION FROM PERITONEAL CAVITY

The intraperitoneal route for blood transfusion has been used by some men, but only in isolated cases.

Ponfick,[6] in 1875, encouraged by his results on animals, injected defibrinated blood into three patients with good results. He injected from 220 to 250 c.c. with only slight febrile reactions. He stated that it acted as a true transfusion and not as the introduction of nutrient material, because he found no hemoglobinuria. However, his conclusions are overdrawn because he did not make any blood counts before and after the transfusion.

---

[19] Lesage, J.: Transfusion sanguine intraperitoneale, Recueil de med. Veterinaire **7**:350 (June 15) 1900; Sur la resorption du sang injecte dans la cavita peritoneale, Compt. rend. Soc. de Biol. **11**:553, 1900.

[20] Skutsch: Die Entstehung der Hämatocoele, Arch. f. Gynäk. **77**:99, 1906.

[21] Buxton, B. H., and Torrey, J. C.: Absorption from the Peritoneal Cavity, J. M. Research. **15**:5 (July) 1906.

[22] Zimmermann, R.: Ueber die Indikationsstellung zur Retransfusion in die Bauchhöhle ergossenen Blutes, Ztschr. f. Geburtsh. u. Gynäk. **84**:334 (Nov.) 1921.

In 1880, Golgi and Raggi[23] transfused an insane person, 38 years of age, with 310 c.c. of defibrinated blood. The hemoglobin rose from 35.8 to 44.1 per cent. in eighteen hours. Fourteen days later, the hemoglobin was 57.9 per cent. No bad effect was noted at any time.

During the same year, Mangiagalli[24] injected 200 c.c. of defibrinated blood into the peritoneal cavity of a woman suffering from hemorrhage following a placenta praevia, with very good results. However, she had another hemorrhage four days later and died.

Mosler,[25] in 1881, warned against the use of the intraperitoneal route because of the danger of peritonitis. He injected 40 c.c. of defibrinated blood in a case of idiopathic anemia without any good or bad results. Encouraged by this, he injected 130 c.c. of blood fourteen days later, and the patient died of acute peritonitis. He thought death was due to the too early repetition of the operation. However, at the necropsy there was no blood in the peritoneal cavity.

Scottini,[26] in the same year, transfused a farmer's wife, aged 45 years, with 270 gm. of defibrinated blood. There was only a transitory improvement. The patient died of anemia one month later.

Giovanni,[27] in 1881, injected 270 c.c. of defibrinated blood into a 9 year old girl, complaining of severe anemia. There was a steady improvement, which reached its climax on the fifteenth day.

Von Kaczorowski,[28] in 1881, reported five cases of transfusion into the abdominal cavity. He used defibrinated blood. No results are given.

Burresi,[29] in 1883, collected thirty-eight cases from the Italian literature and reported a case of his own. In his thirty-eight cases there was improvement in twenty-four, no effect in seven, and a bad effect in seven. He performed a transfusion on a patient with pernicious anemia using 250 gm. of defibrinated blood without any bad symptoms. The patient died six days later.

Liegl,[30] in 1884, reported a case of puerperal hemorrhage in which he injected 175 c.c. of defibrinated blood with good results.

MODE OF ABSORPTION OF BLOOD FROM THE PERITONEAL CAVITY

In 1862, von Recklinghausen[5] noticed a marked injection of the vessels on the pleural side of the diaphragm after the intraperitoneal injection of defibrinated blood. He found that resorption of carmin particles took place only through lymph channels. Urine specimens and serum showed no evidence of red. He covered the rabbit's diaphragm with milk and noticed a series of eddies where the fluid rapidly entered. After marking these places, he treated the diaphragm with silver nitrate and found corresponding black spots between the endothelial cells which he thought were the mouths of the

---

23. Golgi and Raggi: Trasfusione di sangue del peritoneo in un alienato oligocitemico, Gazz. med. ital. **7**:61 (Feb.) 1880; abstr. Jahresb. d. ges. Med. **15**:314, 1880.

24. Mangiagalli: Peritoneale Bluttransfusion, Zentralbl. f. Gynäk., No. 19, p. 463 (Sept. 11) 1880.

25. Mosler, F.: Ueber Gefahren der peritonealen Transfusion, Deutsch. Arch. f. klin. Med. **28**:476 (April 25) 1881.

26. Scottini, P.: Trasfusione di sangue nel peritoneo in una donna malata di grave anemia per anchilostomia, Ann. univ. di med. e chir. **255**:93, 1881; abstr. Jahresb. f. med. Wissensch. **16**:304, 1881.

27. Giovanni, A. de: Un caso di gravissima anemia felicemente mediante la trasfusione di sangue intraperitoneale, Raccolt. da Marzolo, Gazz. med. ital. **24**:39 (Nov.) 1881; abstr. Jahresb. f. d. ges. Med. **16**:240, 1881.

28. Von Kaczorowski: Fünf Fälle von Bluttransfusion in die Peritonealhöhle, Deutsch. med. Wchnschr. **6**:610, 1880.

29. Burresi, P.: Trasfusione sanguigna peritoneale in uno caso di anemia perniciosa, Sperimentale **52**:13, 1883.

30. Liegl: Ueber peritoneale Transfusion, Aerztl. Int.-Bl. **31**:33, 49, 1884.

lymph vessels—his so-called stomata. He concluded that "die tendinösen Theile des Zwerchfelles aus der Bauchhöhle nicht nur Flüssigkeiten resorbieren, welche mit Wasser nicht mischbar sind, sondern auch solche wässerige und ölige Flüssigkeiten, welche kleine Theile suspendirt enthalten."

Auspitz,[31] in 1871, confirmed these results.

Notkin,[32] in 1888, again repeated von Recklinghausen's experiments and further confirmed his results. He dissected out the thoracic duct in dogs and let the lymph flow out. He showed that free erythrocytes are found in the lymph after a period.

In 1893, Beck[33] treated the diaphragm of rabbits with silver nitrate and showed structures on the peritoneal surface of the central tendon which he thought were, without doubt, the openings of the lymph vessels into the peritoneal space. These communications formed short canals, lined with endothelium, which were continuous on one side with the endothelial lining of the peritoneal cavity, and on the other side, with the endothelium of the lymph vessels. After injecting bird's blood into the peritoneal cavity of dogs, and allowing the lymph to escape from the thoracic duct, he demonstrated red blood cells in the lymph in from one to two hours.

Starling and Tubby,[34] in 1894, injected indigo carmin and methylene blue in solution into the pleural and peritoneal cavities of animals, and observed the reappearance of pigment in the urine after ligation of the thoracic duct and after introducing cannulae and collecting the lymph before its entrance into the blood stream. They always found color in the urine before its appearance in the lymph stream, and concluded that there was a direct interchange between the fluid in the cavities and the blood in the vessels. They supported the blood vessel theory of absorption.

Hamburger,[35] in 1895, tied off the thoracic duct to see whether absorption would take place and found that resorption went on, but much more slowly. He concluded that the blood vessels played the more important rôle in resorption from the peritoneal cavity.

Cohnstein,[36] in 1895, from work on three dogs, concluded that isotonic solutions were taken up by the lymph vessels only; hypertonic and hypotonic solutions by the blood vessels.

Muscatello,[37] in 1895, in a very extensive and complete report of this subject, considered the diaphragm as the only point of absorption from the peritoneal cavity. From a large number of microscopic studies he concluded that there are no stomata in the diaphragm. He showed that these stomata are in reality artefacts, and that absorption took place by a process of active diapedesis of the injected particles. He suggested that the erythrocytes make their way between the endothelial cells for the most part in a free condition and only to a smaller degree, as the contents of phagocytes.

Robinson,[38] in 1897, injected a water solution of methylene blue into rabbits and dogs, and thought that he was able to make out stomata in the peritoneum which he held responsible for absorption.

---

[31] Auspitz, E.: Ueber die Resorption ungelöster Stoffe bei Saügethieren, Stricker's med. Jahrb. **3**:284, 1871.

[32] Notkin, J. A.: Vorläufige Mitteilung über Experimente zur Lehre vom Ascites, Wien. klin. Wchnschr. **1**:700 (Nov.) 1888.

[33] Beck, A.: Ueber die Aufsaugung fein vertheilter Körper aus den serösen Höhlen, Wien. klin. Wchnschr. **6**: No. 46 (Nov. 16) 1893.

[34] Starling, E. H., and Tubby, A. H.: On Absorption from and Secretion Into the Serous Cavities, J. Physiol. **16**:140 (Jan.-June) 1894.

[35] Hamburger, H. J.: Ueber Resorption aus der peritonealhöhle, Centralbl. f. physiol. **9**:484, 1895.

[36] Cohnstein, W.: Ueber Resorption aus der Peritonealhöhle, Centralbl. f. physiol. **9**:401, 1895.

[37] Muscatello, G.: Ueber den Bau und das Aufsaugungsvermögen des Peritonäums, Virchows Arch. f. path. Anat. **142**:327 (Nov.) 1895.

[38] Robinson, B.: Observations upon the Absorption of Fluids by the Peritoneum, Ann. Surg. **25**:332 (Jan.-June) 1897.

Meltzer,[39] in 1897, repeated the experiments of Starling and Tubby[34] and found that "colored fluid appeared invariably in lymph distinctly earlier than in urine." He advocated the lymphatic theory of absorption.

Starling,[40] in 1898, repeated his own experiments and obtained his original results.

During the same year Mendel[41] injected indigo carmin in dogs and collected lymph by a cannula in the thoracic duct and urine by a cannula in each ureter. In every case he found that color appeared in the urine long before it could be detected in the lymph of the thoracic duct. He favored the "blood vessel theory" of absorption from the peritoneal cavity.

In a series of papers (1901, 1904 and 1905) Sabin[42] proved conclusively that the lymphatic channels and ducts form a system which has no connection with the large serous cavities of the body. She regarded the lymphatics as modified veins, entirely independent of any openings into central thoracic spaces.

MacCallum,[43] in 1903, after careful microscopic studies of the diaphragm, concluded that the lymphatics were not in direct communication with the peritoneal cavity, but that in places, there was nothing between the two except the endothelial linings of the lymphatics on one side and the lining of the peritoneum on the other, with an exceedingly fine basement membrane between the two layers of cells. He thought that the lymph channels were enlarged at such points and that particles could be forced through by the pumping action of the diaphragm. His results closely confirmed those of Muscatello.[37]

Buxton and Torrey,[21] in 1906, after a large number of experiments, were unable to demonstrate a direct connection between the peritoneal cavity and the lymphatics of the diaphragm. They found, however, that after the intraperitoneal injection of suspensions, there was an "immediate rush of particles to the lymphatics of the diaphragm. From the diaphragm the particles were carried along the anterior mediastinal lymphatic trunks and through the lymph nodes, reaching the thoracic duct and blood current almost immediately after injection."

MATERIAL AND METHODS

With the exception of a few experiments in which the blood of pigeons was used, all our investigations were conducted on rabbits. Details of each series of experiments will be found in their respective order. We were careful to use healthy animals that had not been used for any previous work. A different rabbit was used for each experiment, so that no two transfusions were done on the same animal.

Blood was obtained in a few cases by cardiac puncture, in others, by the insertion of a cannula placed in a carotid, with the subsequent death of the animal.[44]

---

[39] Meltzer, S. J.: On the Paths of Absorption from the Peritoneal Cavity, J. Physiol. **22**:198, 1897.

[40] Starling, E. H.: On Absorption from Peritoneal Cavity, Proc. Physiol. Soc. Lond. **22**:24-26 (Jan.) 1898.

[41] Mendel, L. B.: On Absorption from the Peritoneal Cavity, Am. J. Physiol. **2**:342, 1898.

[42] Sabin, F. H.: On the Development of the Superficial Lymphatics in the Skin of the Pig, Am. J. Anat. **3**:183, 1904.

[43] MacCallum, W. F.: On the Relation of the Lymphatics to the Peritoneal Cavity in the Diaphragm and the Mechanism of Absorption of Granular Materials from the Peritoneum, Anat. Anz. **23**: No. 6 (May) 1903; On the Mechanism of Absorption of Granular Materials from the Peritoneum, Bull. Johns Hopkins Hosp. **14**:105, 1903.

[44] For aid in employing this procedure we are greatly indebted to Dr. R. A. Kriz.

However, we soon found that we were able to obtain blood easily and rapidly by venesection of one of the smaller vessels of the ear, after topical applications of xylol.

Our dosage for transfusion was almost uniformly 10 c.c. of citrated blood, independent of the weight of the recipient, and we were able to get this amount very readily by the foregoing procedure.

All the experiments were performed under aseptic conditions. At the end of each series, the animals were killed and every organ was carefully examined. In some instances, specimens for microscopic examination were taken.

All hemoglobin estimations were made with the von Fleischl-Miescher hemoglobinometer. Both hemoglobin values and erythrocyte counts were checked repeatedly and averages taken. In many cases, the urine and feces were examined for occult blood.

TABLE 1.—Intraperitoneal Transfusion of Whole Blood

Exper. No.	Necropsy	Weight of Animal in Gm.	Quantity Transfused, C.c.	Amount Recovered at Necropsy, C.c.	Remarks
1	1½ hrs.	410	10	10	Clots over omentum, mesentery and in abdominal cavity. No injection of pleural surfaces
2	2 hrs.	920	10	7	No laking; few clots
3	2 hrs.	450	10	10	No absorption; clots. No injection of pleural surfaces
4	2½ hrs.	800	10	10	No absorption; clots
5	3 hrs.	870	10	6	Large clots present. No injection of pleural surface

Presentation of Data

INTRAPERITONEAL TRANSFUSION WITH WHOLE BLOOD

It can be seen from our review of the literature that only defibrinated and whole blood have been used for experimental purposes. We did not attempt to use defibrinated blood because of the greater simplicity with which citrated blood can be obtained. However, in our preliminary experiments we did use whole blood intraperitoneally. All protocols and results obtained are shown in Table 1. In no case were we able to demonstrate absorption of the injected whole blood. In every instance, clots were present in the abdominal cavity at necropsy. The presence of clots in the peritoneal cavity with the subsequent formation of adhesions (Baisch[45]) makes this method inadvisable.

It must be remembered also that the formation of clots means the entanglement of a large proportion of the injected erythrocytes. Coagulation mechanically prevents their absorption, and the very object of their injection is defeated.

---

45. Baisch, K.: Klinische und experimentelle Untersuchungen über postoperativen Ileus, Hegars Beitr. z. Geburtsh. u. Gynäk. **9**:437, 1905.

Furthermore, it is a well known fact, that even in the intramuscular injections of whole blood, rapidity of procedure is vital, because the blood often clots in the syringe. In transfusing relatively large amounts of blood, this difficulty would be enhanced proportionately.

INTRAPERITONEAL TRANSFUSION WITH CITRATED BLOOD: IMPORTANCE OF FRESH SOLUTIONS AND IMMEDIATE INJECTION

We then attempted the use of citrated blood but, at the beginning, with very erratic results. After reviewing our technic, we found that we had overlooked two factors: We were using citrate solution that had not been freshly prepared, and we had allowed our citrated blood to stand three or four hours, and sometimes even over night, before giving it to the recipient. Table 2 shows the results we obtained and the details of each experiment. It can be seen that, though clotting does not take place, there is practically no absorption from the peritoneal cavity, even after long periods of time (Experiment 17). In this series, there is apparent a tendency for an outflow of serum from the circulation into the peritoneal cavity (Experiment 15). This may be an attempt on the part of the body to equalize the difference in osmotic pressure probably present. A comparison with Table 1 shows that this phenomenon does not occur when whole blood is used. Perhaps, the citrate solution, which was not freshly prepared, may account for this difference.

TABLE 2.—INTRAPERITONEAL TRANSFUSION OF CITRATED BLOOD—OBTAINED FROM THREE TO TWENTY-FOUR HOURS PRIOR TO OPERATION

Exper. No.	Necropsy	Weight of Animal in Gm.	Quantity Trans-fused, C.c.	Amount Recovered at Necropsy, C.c.	Remarks
6	30 min.	920	10	10	No laking. Congestion of abdominal side of diaphragm
7	1 hr.	850	10	12	No absorption
8	1 hr.	760	10	10	No absorption
9	2 hrs.	890	10	8	No absorption. No congestion
10	3 hrs.	800	10	13	No absorption. Peritoneum injected
11	3 hrs.	900	10	13	No absorption. No injection
12	3 hrs.	790	10	8	No absorption
13	4 hrs.	620	10	11	No absorption
14	4 hrs.	750	10	10	No absorption. No injection
15	4 hrs.	1,220	10	20	No absorption. Very dilute fluid
16	5 hrs.	820	10	12	No absorption. No injection
17	12 hrs.	900	40	40	No absorption. No injection; very viscous material

Evidence Showing that the Cells Are Absorbed.—(*a*) Examination of Animals at Necropsy Following the Production of a Plethora: Using a uniform technic and preparing fresh solutions each time, we then transfused nineteen rabbits by the intraperitoneal route. Complete data and observations are given in Table 3. We wish to call particular attention to the fact that in those animals showing apparently only little absorption, the fluid obtained at the necropsy did not resemble the blood that we had injected. It was more of the character of blood stained fluid. It can be noted that in every instance in which this occurred (Experiments 24, 25 and 31) the hemoglobin showed a definite rise varying from 8 to 14 per cent. This cannot be accounted for by a concentration of the blood volume and so we must assume that the absorption of erythrocytes is taking place rapidly.

At necropsy, the pleural surface of the diaphragm and the lymphatics leading from it were congested in every case. Smears were made of the peritoneal contents of all animals and in no instance did we find evidence of hemolysis. The cells appeared normal in size, shape and structure. There was no evidence of phagocytosis. A few polymorphonuclear and lymphocytic leukocytes were seen, but these have been shown to be normally present (Kanthack and Hardy[46]). Urine and feces examinations for occult blood and evidence of blood destruction were consistently negative.

TABLE 3.—Intraperitoneal Injection of Freshly Citrated Blood of Normal Rabbits

Exper. No.	Necropsy	Weight of Animal in Gm.	Quantity Transfused, C.c.	Amount Recovered at Necropsy, C.c.	Remarks
18	2 hrs.	720	10	0	Complete absorption; pleural surfaces of diaphragm injected
19	1 hr.	520	10	2	Absorption almost complete; pleural surface of diaphragm injected
20	2 hrs.	460	10	4	Absorption progressing
21	2 hrs.	770	10	..	Subcutaneous blood. No coagulation, no absorption
22	2 hrs.	790	10	0	Absorption complete. Injected lymph vessels
23	2 hrs.	1,120	10	4	Some hemorrhage at operation
24	2 hrs.	850	10	8	Blood fluid; Hb. rose from 57 to 68%. Injection of lymph vessels
25	2½ hrs.	800	10	11	Bloody fluid; Hb. rose from 52 to 66%
26	2½ hrs.	770	10	Few gtt. of blood-stained fluid	
27	2½ hrs.	460	10	0	Complete absorption
28	3 hrs.	800	10	0	Complete absorption
29	3 hrs.	700	10	4	Blood tinged fluid
30	3 hrs.	720	10	0	Complete absorption
31	3 hrs.	800	10	8	Bloody fluid. Hb. rose from 58 to 66% in 2 hours, then fell to 62%
32	4 hrs.	590	10	0	Complete absorption
33	4 hrs.	350	10	5	Small animal
34	4 hrs.	340	10	6	Small clot; smears normal
35	5 hrs.	370	10	0	Complete absorption, nearly ½ of its own blood volume
36	17 hrs.	1,010	15	0	Complete absorption

According to Küttner,[47] the blood volume of a rabbit is approximately from one-nineteenth to one-twentieth of its body weight. On this basis the animal used in Experiment 35 had a blood volume of about 19 c.c. Without producing any anemia, this rabbit received 10 c.c., or one-half of its own blood volume, intraperitoneally. Five hours later, the abdominal cavity showed no evidence of blood. Tests for blood in the urine and feces were negative. This shows clearly the remarkable absorptive capacity of the peritoneal cavity.

---

[46] Kanthack, A. A., and Hardy, W. B.: The Morphology and Distribution of the Wandering Cells of Mammalia, J. Physiol. **17**:81, 1894.

[47] Küttner, H.: Experimentelle Untersuchungen zur Frage des künstlichen Blutersatzes, Beitr. z. klin. Chir. **40**:609 (Nov.) 1903.

We concluded from this study that absorption in an average sized rabbit, when transfused intraperitoneally with approximately one fifth of its own blood volume, is complete in about four hours. There is, of course, a very apparent individual variability.

(*b*) Examination of Animals at Necropsy Following Autotransfusion: Table 4 shows the results obtained after autotransfusion of citrated blood. The amount transfused was taken in every case from the ear of the rabbit and injected immediately into its peritoneal cavity. Unfortunately, we made no blood studies on this group. It would appear that absorption under these conditions takes place more rapidly than in those animals that have not been bled. In these animals an anemia has been produced, and the transfusion is required. In the others, transfused without a preliminary depletion of the blood volume, a plethora is produced, absorption still takes place, but more slowly.

TABLE 4.—INTRAPERITONEAL TRANSFUSION OF CITRATED BLOOD—AUTOTRANSFUSION

Exper. No.	Necropsy	Weight of Animal in Gm.	Quantity Trans-fused, C.c.	Amount Recovered at Necropsy, C.c.	Remarks
37	50 min.	870	10	5	Bloody fluid
38	90 min.	...	8	0	Complete absorption
39	3 hrs.	1,030	10	5	Injury at laparotomy with some bleeding
40	3 hrs.	1,020	10	0	Complete absorption
41	3 hrs.	890	10	0	Complete absorption
42	3 hrs.	870	10	0	Complete absorption

These observations, made at the necropsy table, where accurate data can be obtained, and results noted under direct vision, without the aid of instrumental assistance, show beyond doubt that absorption of citrated blood from the peritoneal cavity does occur. However, the question remains—Are the red blood cells absorbed as red blood cells or are they broken down and merely utilized as nutrient material?

Evidence Showing That the Cells are Absorbed Without Morphologic Changes.—(*a*) Recovery After Transfusion Following the Production of Severe Anemia: In order to determine this point more definitely, we performed the following experiments. Normal healthy rabbits were bled daily, small amounts at a time, until the hemoglobin fell to about 30 per cent. and the erythrocytes count to 3,500,000. Detailed data and mode of procedure are given in Table 5. After

TABLE 5.—INTRAPERITONEAL TRANSFUSION OF CITRATED BLOOD AFTER PRODUCTION OF SEVERE ANEMIA

Exper. No.	Weight of Animal in Gm.	Original Blood Examination		Blood Picture Before Transfusion		Amount Injected in C.c.	Blood Picture Following Injection									
							1st Day		2d Day		3d Day		4th Day		5th Day	
		Hb %	R.B.C.	Hb. %	R.B.C.		Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.
43	1,000	53	5,580,000	30	3,000,000	18	33	3,360,000	35	3,170,000*	..	....	..	....	..	....
44	1,140	55	5,400,000	28	2,950,000	22	29	3,060,000	..	....	34	3,520,000	..	....	35	3,900,000
45	1,050	54	5,870,000	31	3,200,000	31	37	3,860,000	..	....	39	4,270,000	..	....	41	4,470,000
46	1,150	54	5,500,000	36	3,800,000	25	42	4,500,000	41	4,250,000	..	....	44	4,350,000	49	4,980,000
47	1,030	58	5,450,000	32	3,320,000	18	44	4,610,000	45	4,630,000	46	5,100,000	..	....	56	5,900,000

* Animal died on 7th day.

TABLE 6.—SUBCUTANEOUS INJECTION OF CITRATED BLOOD FOLLOWING PRODUCTION OF ANEMIA

Exper. No.	Weight of Animal in Gm.	Original Blood Examination		Blood Picture Before Transfusion		Amount Injected in C.c.	Blood Count Following Injection							
							1st Day		3d Day		5th Day		7th Day	
		Hb. %	R.B.C.	Hb. %	R.B.C.		Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.
48	1,050	58	5,250,000	29	3,100,000	15	30	3,170,000	33	3,980,000	32	3,630,000	32	3,630,000
49	950	53	5,420,000	30	3,340,000	20	31	3,380,000	31	3,880,000	25	3,920,000	25	3,490,000
50	1,000	56	5,300,000	34	3,300,000	20	32	3,400.000	34	3,500,000	34	3,340,000	35	3,400,000

TABLE 7.—INTRAPERITONEAL TRANSFUSION OF CITRATED BLOOD, AFTER PRODUCTION OF ANEMIA, SHOWING BLOOD CHANGES

Exper No.	Weight of Animal in Gm.	Blood Before Experiment		Blood Before Transfusion		Amount In-jected, C.c.	Blood Picture Following Injection														Remarks
							1 Hour		3 Hours		4 Hours		2 Days		3 Days		6 Days		11 Days		
		Hb. %	R.B.C.	Hb. %	R.B.C.		Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	
51	1,050	58	5,250,000	32	3,630,000	25	41	4,280,000	36	4,120,000	35	4,040,000	42	4,860,000	42	4,860,000	..	....	..	....	
52	1,040	55	5,400,000	41	4,050,000	22	48	5,760,000	47	5,840,000	43	4,700,000	47	5,150,000	54	5,960,000	54	5,490,000	56	5,500,000	Moderate anemia
53	980	56	5,300,000	38	4,000,000	20	47	5,400,000	45	5,500,000	42	5,100,000	46	5,390,000	51	5,670,000	53	5,540,000	52	5,600,000	Moderate anemia

TABLE 8.—INTRAPERITONEAL TRANSFUSION OF CITRATED BLOOD, IN NORMAL ANIMALS, SHOWING BLOOD CHANGES

Exper. No.	Weight of Animal in Gm.	Blood Before Injection		Amount Injected, C.c.	Blood Counts Following Injection															
					1 Hour		3 Hours		2 Days		3 Days		4 Days		5 Days		6 Days		9 Days	
		Hb. %	R.B.C.		Hb %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.
54	1,440	50	5,470,000	22	67	6,560,000	72	8,330,000	65	7,140,000	68	6,150,000	62	6,390,000	..	....	60	5,730,000	60	5,800,000
55	1,150	55	5,250,000	21	67	6,300,000	67	6,850,000	67	6,540,000	68	6,700,000	69	6,800,000	..	....	67	6,500,000	..	....
56	1,350	51	5,400,000	16	60	6,480,000	63	6,370,000	57	5,730,000	60	5,700,000	..	....	59	5,390,000	..	....	..	....

TABLE 9.—SHOWING SPONTANEOUS RECOVERY FOLLOWING PRODUCTION OF SEVERE ANEMIA

Exper. No.	Weight of Animal in Gm.	Original Blood Picture		Blood Picture Following Last Hemorrhage		Blood Counts Following Injection													
						1 Day		3 Days		5 Days		7 Days		8 Days		9 Days		14 Days	
		Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.	Hb. %	R.B.C.
57	1,040	55	5,400,000	29	3,730,000	33	3,630,000	..	....	38	4,440,000	41	4,050,000	..	....	44	5,500,000	..	....
58	950	54	5,390,000	30	3,030,000	30	3,040,000	36	4,180,000	45	4,420,000	..	....	45	5,400,000	..	....	44	5,140,000
59	980	55	5,370,000	28	3,560,000	30	3,360,000	..	....	32	4,100,000	40	4,350,000	..	....	43	4,480,000	..	....

producing this severe anemia, varying amounts of citrated blood were injected into the abdominal cavity and blood examinations were made on the days indicated in the table. It will be seen that in three cases (Experiments 45, 46 and 47) there was a definite rise in hemoglobin estimations and blood counts, which persisted as long as the animals were under observation. In the three animals that responded, the hemoglobin increased from 31, 36 and 32 per cent. to 41, 49 and 56 per cent., respectively, in five days time. There appears to be a sharp rise in blood values following the transfusion. We know from our previous work that the transfused blood enters the circulation approximately in from three to four hours, and that the peritoneal cavity at that time is free of blood. Therefore, it is reasonable to assume that the rise in blood values is due to the fresh erythrocytes that enter the blood stream.

It may be noted that these animals did not react well. This may possibly be explained by the severe blood loss, amounting in some instances (Experiments 46 and 47) to 25 c.c., or almost one-half the total blood volume (Küttner[47]).

(*b*) Detailed Study of Blood Changes During the Absorption Period: From our postmortem studies we were led to suspect that changes occur during the period immediately following the introduction of the blood into the peritoneal cavity. We, therefore, produced a relatively mild anemia in three rabbits and made blood examinations at short intervals for four hours following the operation. Then the blood of these animals was examined over a period of days, as indicated in Table 7. The same procedure was performed also on three rabbits that were not bled, and in whom it was desired to produce a plethora (Table 8).

A comparison of the results is of interest. It can be seen that in the anemic animals there is a sharp rise at the end of the first hour. This initial rise is followed by a fall both in hemoglobin content and red blood cell count during the fourth hour. The gradual rise described by Hunter[16] and the subsequent fall on the second day, which is followed by a more permanent increase, reaching a maximum on the fifth or sixth day, are not confirmed by our experiences. On the second day the blood picture shows distinct improvement in every case, although it never reaches the peak attained at the end of the first hour. This is followed by a slow, gradual fall, yet at the end of nine days the hemoglobin and blood values are still distinctly improved over the initial counts.

In the control series (Table 8) in which a plethora is produced, the same characteristic initial rise at the end of the first hour can be observed. We were unable to get sufficient data to show the secondary fall which we believe does occur. The next day, the blood picture is improved but again does not reach the values attained on the day of the operation. The tendency for the body to adjust itself and regain its normal blood volume by overcoming the plethora is well shown in the more rapid decline in the blood curve (Figs. 1 and 2).

Whether the initial rise in the blood curve in these animals is due merely to a concentration of blood volume or to an actual absorption of the transfused cells is, of course, debatable. The rapid disappearance of the blood injected into the peritoneal cavity shown in Tables 3 and 4, and the fact that, in most cases, the residue still remaining at necropsy is steadily declining in amount are of significance. From our observations, gained at necropsies made on many animals, we incline to the opinion that the former factor plays a subordinate part.

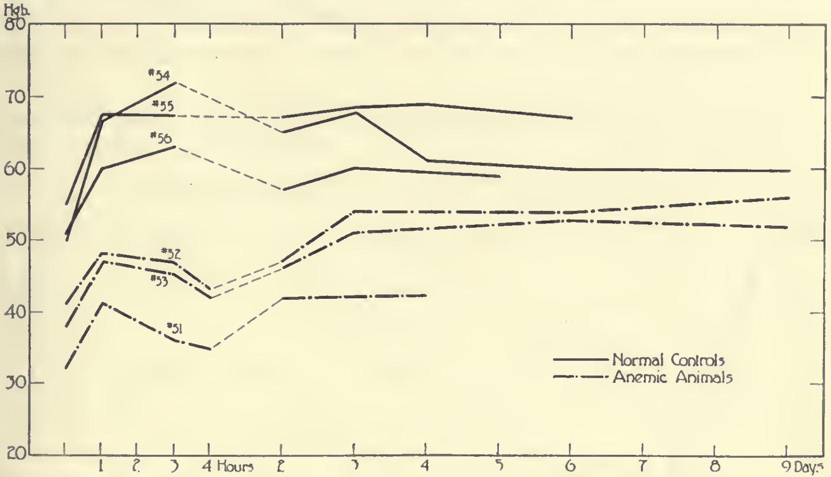


Fig. 1.—Graphic presentation of Tables 7 and 8 showing hemoglobin curve.

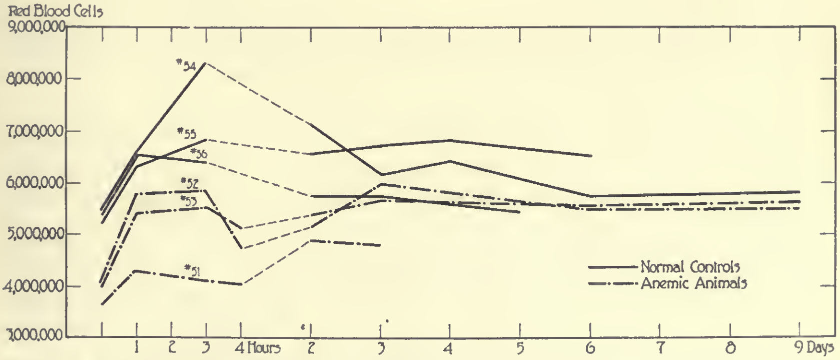


Fig. 2.—Graphic presentation of Tables 7 and 8 showing erythrocyte curve.

Furthermore, a careful study of our material shows that there is a tendency for the red blood cell count to remain high and the drop in hemoglobin is greater than the fall in erythrocytes. This ought not to be the case if a concentration of the blood volume is the dominant factor.

Tables 7 and 8 are presented in graphic form in Figures 1 and 2 in order to show the changes more clearly.

Another factor of importance is the behavior of the animals themselves. Immediately following the operation they act normally, and, throughout the entire experiment, they do not behave any differently from our normal controls. If toxic products are being produced and absorbed, some subjective phenomena should be present. If hemolysis of the cells is taking place, the urine should give a positive benzidin or guaiac reaction.

These results, we think, are sufficient to warrant the conclusion that the cells are absorbed as such. But in order to show beyond doubt that this does occur, we performed the following experiments.

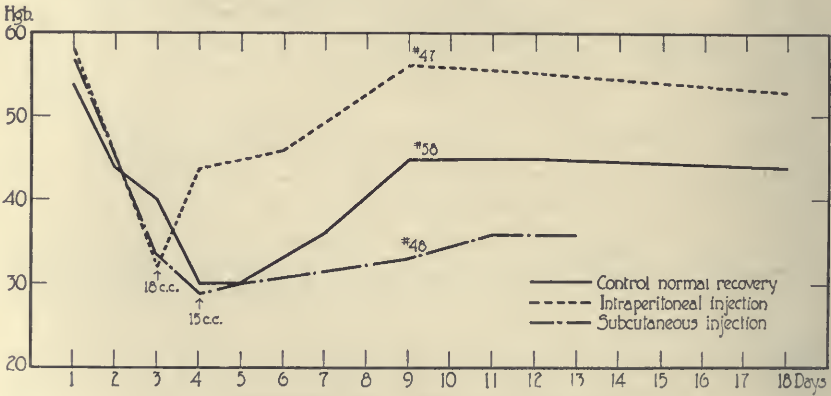


Fig. 3.—Comparison of methods; hemoglobin curve.

(*c*) Recovery of Pigeons' Cells from the General Circulation of Rabbits: Several pigeons were exsanguinated, and the blood was citrated. The citrated blood was then injected into the peritoneal cavity of rabbits. Smears were taken from the blood of the rabbits' ear at fifteen minute intervals for several hours, then daily for the next few days. We were able to demonstrate very clearly the elongated, nucleated red blood cells of the pigeon in the general circulation of the rabbit in fifteen minutes. These cells can still be found after twenty-four hours; but, in the specimens studied thus far, none were encountered later than thirty hours after the injection. These experiments show two things of supreme importance: First, the viability of the erythrocytes is demonstrated. Second, the red cells can pass from the peritoneal cavity into the general circulation without undergoing any morphologic changes.

Evidence Showing That the Cells Function.—At the present time we cannot present any positive evidence that the cells function after their entrance into the blood stream. It appears reasonable, however, to expect that they meet the same fate that awaits red blood cells injected intravenously.

Boycott,[48] in 1910, working on rabbits, determined the total oxygen (hemoglobin) by Welcher's method and drew the following conclusions:

1. Blood transfused into the peritoneal cavity and subsequently absorbed into the circulation is destroyed more quickly than blood transfused by direct intravenous injection.
2. It is suggested that this difference is due to the red blood cells being rendered relatively more foreign by their passage through an extravascular position.
3. The mechanism of destruction is the same, except that phagocytosis of red cells in the lymphatic glands and spleen is much more prominent than with intravenous transfusion.

This work has never been confirmed. It may be noted that Boycott assumes that there is rapid destruction of cells introduced intravenously.

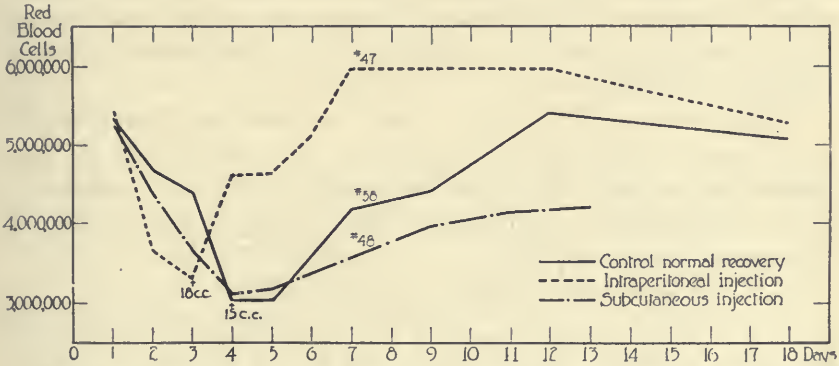


Fig. 4.—Comparison of methods showing value of intraperitoneal blood transfusion after production of severe anemia; erythrocyte curves.

Ashby[49] has recently proved "that the life of the transfused corpuscle is long." She states that "the beneficial results of transfusion are without doubt not due primarily to a stimulating effect on the bone marrow, but, it is reasonable to assume, to the functioning of the transfused blood corpuscles."

We may assume that our injected corpuscles do function because of the persistent, fairly permanent rise in blood values in anemic animals, following the transfusion, and because we have been unable to find any evidence, either from a laboratory or clinical standpoint, showing destruction of cells. In a subsequent paper we hope to present further data affording more conclusive proof that the erythrocytes function.

---

48. Boycott, A. E.: Peritoneal Blood Transfusion, J. Path. & Bacteriol. **14:** 605, 1909.

49. Ashby, W.: The Determination of the Length of life of Transfused Blood Corpuscles in Man, J. Exper. M. **29**:267 (March) 1919.

COMPARISON OF SUBCUTANEOUS AND INTRAPERITONEAL INJECTIONS OF CITRATED BLOOD

In order to compare the relative merits of the subcutaneous injection of citrated blood with the intraperitoneal transfusion, we produced an anemia in a series of rabbits, according to the method already described, and injected varying amounts of blood subcutaneously. Data and details of the experiment are given in Table 6. It can be seen that in no case was there any suggestion of a rise either in hemoglobin or in the erythrocyte counts. Even on the seventh day, there was no marked change in the blood picture. At the necropsy on these animals, a week later, there were present subcutaneous clots at the site of the injection.

A comparison with Table 9 reveals that the animals used as controls recovered from their anemia more rapidly than those receiving subcutaneous blood. The obvious conclusion is that the subcutaneous injection of citrated blood actually hinders the recuperative process. This is contrary to all of our teachings, and at present we have no explanation to offer.

While working with pigeon's blood, we took the opportunity to inject some of that blood subcutaneously into rabbits with the purpose of demonstrating the corpuscles in the circulation of the animal—if they are absorbed. Smears were taken at fifteen minute intervals for several hours, then every day for several days. In no case were we ever able to find pigeons' blood cells in the blood stream.

It would seem from this that the cells injected subcutaneously do not enter the general circulation, at least in any appreciable number. This confirms, in a striking way, the results obtained by Taylor.[50]

COMMENT

The Intraperitoneal Injection in General.—The intraperitoneal method of approach has been shown to be relatively safe by many men, Blackfan and Maxcy,[51] McLean and Lang,[52] Denzer and Anderson,[53] Gittings and Donnelly,[54] and others. At present the intraperitoneal injection of normal saline or glucose solution in dehydrated and athreptic infants is a recognized therapeutic procedure (Marriott[55]). The injection of citrated blood offers no greater technical difficulties than does that of physiologic sodium chlorid solution.

---

[50] 50. Taylor, R.: The Fate of Subcutaneously Injected Red Blood Cells, Am. J. Dis. Child. **20**:337 (Oct.) 1920.

[51] 51. Blackfan, K. D., and Maxcy, K. F.: The Intraperitoneal Injection of Saline Solution, Am. J. Dis. Child. **15**:19 (Jan.) 1918.

[52] 52. McLean, S., and Lang, C. A.: Fluid Injection in Dehydrated Infants, Am. J. Dis. Child. **19**:359 (May) 1920.

[53] 53. Denzer, B. S., and Anderson, A. F.: The Absorption of Fluids Injected Into the Peritoneal Cavity, Am. J. Dis. Child. **21**:565 (June) 1921.

[54] 54. Gittings, J. C., and Donnelly, J. D.: The Clinical Value of Intraperitoneal Injections of Salt Solution, Am. J. Dis. Child. **23**:124 (Feb.) 1922.

During the course of our investigations we had occasion to use more than 100 rabbits. Intraperitoneal injection done without any special precautions was absolutely harmless. We never had any ill results. Evidence of adhesions or peritonitis was never noted.

The question as to whether the presence of blood in the peritoneal cavity is harmful or not is, of course, of supreme importance. Experimental data collected from all sources seems to indicate that there is no harm from blood in the abdominal cavity. It is true, however, that when whole blood was injected, numerous investigators found clots present when the animal was examined at necropsy.

Is the Presence of Blood in the Peritoneal Cavity Harmful?—Clinicians are very much divided as to the value of blood in the peritoneal cavity, resulting from an ectopic pregnancy or trauma. One group does not remove any blood at the time of operation; another school removes all the blood possible. The third and largest group takes a median course and removes only the clots present at the time of surgical interference.

Zweifel,[56] in 1903, in reporting twenty-one cases of ruptured ectopic pregnancies, concluded that it was dangerous to trust blood in the peritoneal cavity because blood made an excellent medium for bacterial growth.

Füth,[57] in 1905, reviewed the literature thoroughly and concluded that blood should always be removed.

Baisch,[45] in 1905, after a number of experiments on rabbits and from clinical observations, made the following statement: "Die wichtigste Rolle aber in der Aetiologie der Darmverwachsungen spielt, wie unsere Experimente unzweifelhaft und eindeutig ergeben, die Anwesenheit von Blut."

Werth,[58] is of the opinion that leaving a large amount of decomposable material in the peritoneal cavity was not proper from an aseptic standpoint, in the first place; and that even aseptic decomposition products of dying cells had poisonous properties.

Fehling,[59] Haim and Lederer[60] support these views.

Bröse,[61] in a series of papers, dating from 1891 to 1912, reported cases ending in death and in which at necropsy there was no evidence of sepsis or

---

55. Marriott, W. McKim: Some Phases of the Pathology of Nutrition in Infancy, Am. J. Dis. Child. **20**:461 (Dec.) 1920.

56. Zweifel, P.: Zur Behandlung der Hämatocelen, München. med. Wchnschr. **50**:1449 (Aug.) 1903.

57. Füth, H.: Ueber die Behandlung des intraperitonealen Blutergusses nach Tubenrupturen, Zentralbl. f. Gynäk., No. 43, p. 1315 (Oct. 28) 1905.

58. Werth: Die Extrauterinschwangerschaften, V. Winkels' Handb. d. Geburtsh. **2**:938, 1887.

59. Fehling, H.: Grundsätze und Erfahrungen in der Behandlung der Tubenschwangerschaft der frühen Monate, Arch. f. Gynäk. **92**:3 (Oct. 19) 1910.

60. Haim, E., and Lederer, Oskar: Erfahrungen über rupturierte Extrauterinschwangerschaft mit freiem Bluterguss in die Bauchhöhle, Monatschr. f. Geburtsh. u. Gynäk. **25**:1, 207, 1907.

61. Bröse, P.: Ueber die Giftigkeit des in die freie Bauchhöhle ergossenen Blutes, Ztschr. f. Gynäk., No. 35, Pt. 2, p. 1334, 1911; Ztschı. f. Geburtsh. u. Gynäk. **21**:211, 1891.

peritonitis, just blood in the cavity. In his opinion this pointed to a toxic absorption of decomposition products. He concluded that blood in the abdominal cavity should be considered as dead tissue of no use to the patient and at times very dangerous. He thought the fluid portion was especially toxic. In a later paper he suggested that the body may have developed a sort of anaphylaxis against its own proteins.

In 1911, Bumm[62] confirmed these results.

Löwenstein,[63] in 1911, reported two cases supporting Bröse's view as to the toxicity of the blood in the peritoneal cavity.

Els,[64] in 1913, advocated the complete removal of all blood from the peritoneal cavity. In thirty-one cases of ruptured ectopic pregnancies, he had one death. He thought the rise in temperature was due to absorption of blood and the rise in pulse to absorption of toxic products of decomposition. He found that the pulse and appearance of the patient improved after removal of blood.

On the other hand, men of equal ability urge the harmlessness and the value to be derived from leaving the blood alone. Veit,[65] Ekstein,[66] Frommel,[67] Flatau,[68] and others, leave everything in the abdominal cavity with good results. V. Franque[69] reports sixty-seven cases without any fatalities.

Most men, however, take the middle course, removing clots and leaving the unclotted blood to be reabsorbed. Olshausen, Gusserow,[70] Hannes,[71] Fritsch,[72] Hörrmann,[73] Fiedler,[74] Wagner,[75] Runge,[76] Zimmermann,[22] and others, remove only the large clots in the abdominal cavity.

---

62. Bumm, E.: Ueber die peritoneale Wundbehandlung. Was verträgt das Peritoneum, was nicht? Monatschr. **34**: (Aug.) 1911; Ztschr. f. Geburtsh. u. Gynäk. **70**:2, 312, 1911.

63. Löwenstein: Ueber die Giftigkeit des in die freie Bauchhöhle ergossenen Bluts, Med. Klin. **7**:1773, 1911.

64. Els, H.: Ueber die Giftigheit und Gerinnungsverzögerung des intraperitonealen Blutergusses nach Tubenruptur, Arch. f. Gynäk. **99**:167, 1913.

65. Veit, J.: Doederlein's Handb. d. Geburtsh. **2**: 1916. (Quoted by Lichtenstein.[82])

66. Ekstein, E.: Zur Kenntnis der Tubenschwangerschaft, Monatschr. f. Geburtsh. u. Gynäk. **5**:140, 1897.

67. Frommel: Zur Therapie und Anatomie der Tubenschwangerschaft, Deutsch. Arch. f. klin. Med. **45**: 1889.

68. Flatau: Muss bei der Operation geplatzter Extrauterinschwangerschaften des in die Peritonealhöhle ergossenen Blutes entfernt werden, München. med. Wchnschr., No. 2, p. 42 (Jan.) 1904.

69. Franque, V.: Ueber Blutungen in die freie Bauchhöhle bei Extrauterinschwangerschaft, Prag. med. Wchnschr., 1904, p. 295.

70. Gusserow, A.: Ueber hochgradigste Anämie Schwangerer, Arch. f. Gynäk. **2**: 1871.

71. Hannes: Die Notoperationen bei Extrauteringravidität, Prakt. Ergebn. der Geburtsh. **14**:3, 1909.

72. Fritsch: Die retrouterine Hämatocoele, Samml. klin. Vortr. **19**:449, 1875.

73. Hörrmann, A.: Zur Klinik und zur Therapie der ectopischen Schwangerschaft, Ann. d. Städt. allg. Krankh. z. München. **12**:246, 1907.

74. Fiedler: Beitrag zur Aetiologie, Diagnostik und Therapie der Tubargravidität, Deutsch. Ztschr. f. Chir. **95**:170 (Nov.) 1908.

75. Wagner, A.: Zur Behandlung der geplatzten Extrauteringravidität mit freier Blutung, Deutsch. med. Wchnschr. **38**:1457 (Aug.) 1912.

76. Runge: Beitrag zur Aetiologie, Symptomatologie und Therapie der Extrauteringravidität, Arch. f. Gynäk. **70**:690, 1903.

Clinical opinion is divided, but a review of the literature clearly shows that most men obtain excellent results by removing only the clots present in the abdominal cavity. The consensus of opinion appears to be that the fluid portion remaining is not only harmless, but it is also reabsorbed and is of distinct value (Zimmermann [22]).

However, the dangers of clotting with its subsequent results (Baisch [45]) must be borne in mind. It has been shown that clotting does not take place when a freshly citrated solution is used. The constant motion of the intestines resulting from peristaltic movements is probably an important factor in preventing the coagulation. We believe that the actual presence of fluid blood in the peritoneal cavity is without danger.

Clinical Observations as to the Value of Blood in the Abdominal Cavity.—Clinical experience shows the benefit of blood in the peritoneal cavity. It is a well known fact that women who have lost large quantities of blood following a ruptured tube as a result of an ectopic pregnancy recover astonishingly well. Similarly, in cases reported in the literature of ruptured liver or spleen, recovery apparently occurred very quickly from the anemia following the severe blood loss. On the other hand, patients who have suffered severe external hemorrhages from external injuries do not do so well or recover from their anemia so rapidly. In the one case, the hemorrhage is internal; in the other, external. In the former case, the blood can reenter the blood stream and function; while, in the latter case, there is a total loss of blood to the body.

Clinical experience shows that the blood is nontoxic. In 1914, Thies [77] suggested the retransfusion of blood found in the peritoneal cavity in cases of trauma. During the war Elmendorf,[78] Peiser,[79] Kreuter,[80] Ranft,[81] and others, utilized this method on injured soldiers with very good results. Lichtenstein [82] made use of this procedure in cases of ruptured ectopic pregnancies with good results. He reported

---

77. Thies, J.: Zur Behandlung der Extrauteringravidität, Ber. a. d. gynäk. Gesellsch. Zentralbl. f. Gynäk. **38**:1191 (Aug. 22) 1914.

78. Elmendorf: Ueber Wiederinfusion nach Punktion eines frischen Hämatothorax, München. med. Wchnschr., No. 1, 1917, p. 36, quoted by Lichtenstein: Arch. f. Gynäk. **109**:599, 1918.

79. Peiser, A.: Ueber Eigenbluttransfusion bei Milzzerreissung, Zentralbl. f. Chir. **44**:71 (Jan. 27) 1917.

80. Kreuter, E.: Ein weiterer Fall von Wiederinfusion einer intraabdominellen Massenblutung bei Leberruptur, Zentralbl. f. Chir. **44**:765 (Aug. 25) 1917; Zur Wiederinfusion abdomineller Blutungen, München. med. Wchnschr., No. 42, p. 1498 (Oct. 17) 1916.

81. Ranft, G.: Autotransfusion nach Milzruptur, Zentralbl. f. Chir., No. 47, p. 1019 (Nov. 24) 1917.

82. Lichtenstein, F.: Ohne Eigenbluttransfusion sollte keine wegen Tubenusur operierte Frau mehr an Verblutung sterben, Arch. f. Gynäk. **109**:599, 1918.

twenty-seven cases of retransfusion collected from the literature. This would seem to indicate that the possibility of the formation of toxic products in the blood is of comparatively slight consequence.

Evidence gathered from every available source points to the absorptive powers of the peritoneal cavity and to the value of blood in the abdominal cavity. We believe that this knowledge can be utilized clinically. The simplicity of the technic makes the intraperitoneal transfusion the method of choice in selected cases. It affords the only feasible method for the transfusion of large amounts of blood in children more than 18 months of age. The exposure of a vein in the elbow for direct intravenous transfusion is an operation that, for obvious reasons, frequently fails in the hands of the most skilful surgeon. The proposed method can be used by any one. It is rapid, simple and efficient.

SUMMARY

1. We have shown that freshly citrated blood injected into the peritoneal cavity of rabbits is absorbed because: (*a*) Necropsies at various intervals following the operation reveal that the quantity present in the abdominal cavity rapidly decreases in amount and that absorption of comparatively large amounts of blood is complete in three to four hours; (*b*) estimations of blood values demonstrate definite increases from the time the blood is transfused until the animal is killed.

2. We have shown that the erythrocytes enter the blood stream without undergoing any morphologic changes, because: (*a*) Smears of the fluid in the abdominal cavity taken at necropsy show no change in the size, shape or structure of the corpuscles and no evidence of hemolysis; (*b*) our experiments show a rise in hemoglobin and cellular elements following transfusions in normal and anemic animals which cannot be accounted for by a mere concentration of the blood; (*c*) nucleated red blood cells of pigeons when injected intraperitoneally into rabbits can be recovered from the general circulation in fifteen minutes, and can persist there for at least twenty-four hours.

3. We submit the following additional evidence that the erythrocytes function: (*a*) They enter the blood stream very rapidly and are therefore presumably in a functioning condition; (*b*) the increase in the blood values of our animals persisted for days; (*c*) after severe hemorrhage, the animals improved visibly following the transfusion; (*d*) no hemoglobinuria could be demonstrated at any time; (*e*) autotransfusion and retransfusion have been used successfully in man; (*f*) clinical experience with cases of internal hemorrhage as compared with external hemorrhage tends to show that the blood is reabsorbed in a functioning condition.

CONCLUSIONS

1. The intraperitoneal transfusion of citrated blood in rabbits is a safe procedure, simple to apply and efficient.

2. Absorption of blood from the peritoneal cavity of rabbits takes place very rapidly. A rabbit can apparently absorb approximately one fifth of its own blood volume in four hours.

3. The intraperitoneal transfusion in both anemic and normal animals causes a sharp, temporary rise in blood values during the absorptive period. This is followed later by a more permanent increase in the blood picture.

4. Studies at necropsy when considered with the blood counts would apparently indicate that the initial rise is due to an actual absorption of red blood cells from the peritoneal cavity, and not merely to a concentration of the blood volume.

5. Pigeon's blood injected subcutaneously in rabbits apparently does not enter the general circulation in demonstrable amount. The same blood injected intraperitoneally is absorbed very rapidly.

6. The intraperitoneal transfusion of freshly citrated blood acts as a true transfusion and not as the absorption of a nutrient material.

7. The intraperitoneal route for blood transfusions is proposed as a therapeutic method of merit.

CLINICAL APPLICATION

A. W., aged 2, was admitted to the hospital, Aug. 22, 1922, because of poor appetite, weakness and marked pallor since birth.

Physical examination was essentially negative.

Blood examination revealed hemoglobin, 38 per cent. (von Fleischl-Miescher) and a red cell count of 3,600,000. The blood Wassermann reaction was repeatedly negative.

On the tenth day, after the failure of medical treatment, he received 50 c.c. of citrated blood intraperitoneally. The hemoglobin and erythrocyte counts rose materially. Seven days later, he received 100 c.c. of citrated blood. The hemoglobin went up to 52.5 per cent., the erythrocyte count to 5,800,000. Six days later, another transfusion of 100 c.c. of blood was given intraperitoneally. The hemoglobin then was 63 per cent.; erythrocytes, 6,060,000.

The patient was discharged Oct. 10, 1922, showing marked clinical improvement. The hemoglobin was 70 per cent.; erythrocytes, 5,700,000.

CONGENITAL MALARIA

REPORT OF A CASE IN COLORADO *

R. P. FORBES, M.D.
DENVER

In a malarial community, cases of intra-uterine infection with the malarial parasite are rare. In fact, the possibility of such infection is denied by some authorities, although admitted by the majority. The occurrence of malaria in an infant, aged 7 weeks, would invariably be accepted as a postnatal infection in a malarial community. However, the anopheles mosquito has not been found in eastern Colorado, although Cockerell [1] has made a thorough search for the insect in this region. The possibility that an occasional anopheles could be brought to Denver on a train from Texas cannot be denied, but such a circumstance, especially in the case cited, seems very unlikely.

REPORT OF CASE

History.—Baby S., aged 7 weeks, was first seen, Nov. 14, 1921, on account of fever and restlessness. The patient was the second child, the first having died of pneumonia, one year previously. Both parents, born in Greece, asserted that their general health was good. There had been no miscarriages; the mother had had no illness or history of fever during this pregnancy, and at term, Sept. 28, 1921, was delivered of a 7 pound girl baby after a normal labor. The baby was said to have been blue at birth, but otherwise she was normal. It slept well and nursed well, gaining in weight for seven weeks.

Examination.—The patient was well developed, well nourished and of good color and weighed 9 pounds. The temperature was 100.8 F. Examination of the heart, lungs, throat and ears failed to account for the fever. For the following forty-eight hours, the baby seemed to feel better, but November 17 its temperature was 103.6 F. Physical examination was again negative. The urine was free from albumin, pus or bacteria. Another urinalysis and also a Pirquet test proved negative.

Course.—The patient had six febrile attacks at seventy-two hour intervals, before the periodicity was fully appreciated, and the parents were questioned as to a history of malaria. The mother then gave a history of an unusually severe quartan infection in Greece, seven years before, but asserted that she became free from all symptoms three months after coming to the United States in 1916.

December 5, the baby had its seventh febrile attack. The temperature was 103.2 F. It looked anemic; the hemoglobin was 40 per cent.; leukocytes, 5,850; erythrocytes, 3,440,000. The spleen was palpable 2 cm. below the costal margin. The patient was admitted to the Children's Hospital for further study and

---

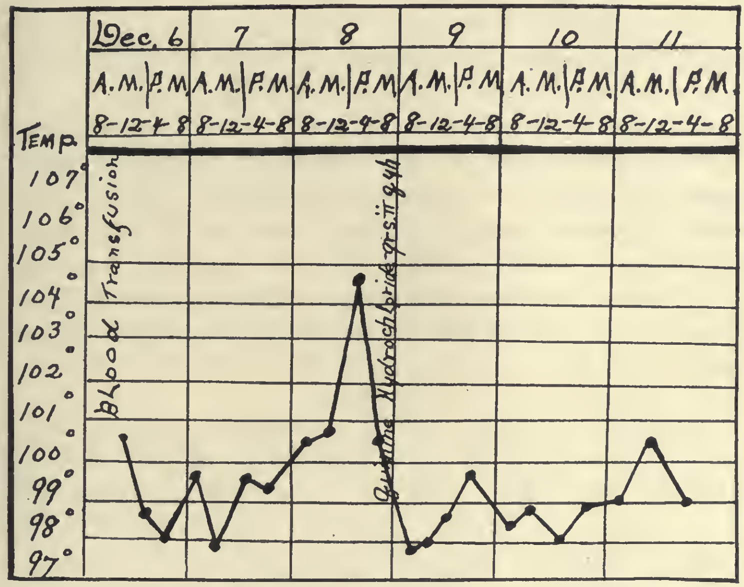
* Received for publication, Nov. 18, 1922.

* From the Department of Pediatrics, University of Colorado School of Medicine.

[1] Cockerell, T. D. A.: The Mosquitoes of Colorado, J. Economic Entomol. **11**:195, 1918.

transfused with 110 c.c. of citrated blood from the father. Blood smears, taken at from twelve to twenty-four hour intervals, demonstrated large numbers of the malaria plasmodia in all stages of the asexual life cycle. On examination, the mother's blood at this time also showed quartan parasites. However, her spleen was not palpable.

Treatment.—On the morning of December 8, the parasites were full grown, the temperature rose to 104.6 F. Quinin hydrochlorid, 2 grains every four hours, was begun after this paroxysm and continued for four days; then it was given three times daily for four days, then three times on each of two days of each week for two months. Twenty days after quinin therapy was begun, the spleen could not be palpated. The baby had gained 26 ounces in fourteen days. At six months, the baby weighed 16 pounds, and had been free from any symptoms of malaria since treatment was begun.



Temperature curve before and after administration of quinin.

COMMENT

In 1910, Beekel [2] reported a case of malaria in early infancy, occurring in Cleveland, which is not in a malarial district, although the anopheles mosquito is found in Ohio. Beekel's case has many striking similarities to the case here reported. In his case the onset of malaria apparently occurred in the seventh week. The parents were of Hungarian origin, and both had suffered from malaria in Hungary, but had been free from symptoms for many years. Both had palpable spleens; but the organisms could not be found in their blood, although the patient's blood contained large numbers of quartan parasites until quinin was given. Beekel reviewed the literature to 1910, quoting twenty authorities, and found twelve cases of undoubted placental transmission. The accepted cases were those of Duschek,[3] Bohn,[4] Meara,[5] Crandall,[6] each one case, Hitte[7] two cases, and Economo[8] six cases. Economo found the parasites in the blood within forty-eight hours after birth, but some of his patients did not develop fever or symptoms. Economo concludes that the manifestations of the disease do not appear in the infant unless the mother had malaria during the latter part of pregnancy.

---

[2] Beekel, Fred.: Report of a Case of Malaria in Early Infancy, Cleveland M. J. **9**:879 (Nov.) 1910.

Since 1910, fifteen conclusive cases of congenital malaria have been reported. Bass[9] reports a case, occurring in midwinter in New York City, in a 4 weeks old baby, whose mother had a tertian infection during the fifth month of pregnancy. Postnatal infection is excluded by Bass on account of the season and location.

A summary of the reported cases shows that (1) all patients did not have symptoms when the plasmodia were found soon after birth, (Economo; Lamaire, Dumolard and Laffont[10]); (2) symptoms appeared at varying ages, the longest postnatal interval being seven weeks (Beekel;[2] Meara[5] and Bass[9]).

It is, therefore, reasonable to suppose that a new-born child can have a relatively latent type of malaria, and that some, at least, of the cases of malaria in infancy hitherto attributed to postnatal infection were, in reality, acquired in utero or at birth.

The method of infection cannot be explained satisfactorily. Bass believes that infection probably occurs at birth, since, if the fetus had been infected for a period of several weeks or months, there would be signs of cachexia at birth. Thayer, Pezopoulos and Cardamitis, Marchiafava, Bignami, and others deny intra-uterine infection from pathologic studies which failed to reveal the plasmodia in the fetal blood, in the cord, or on the fetal surface of the placenta, although the maternal blood contained parasites. However, the cases of Bohn, Pennato and Duschek, in which the stillborn fetus contained evidences of recent infection, show that intra-uterine infection actually may occur.

---

[3] Duschek, quoted by Bohn: Jahrb. f. Kinderh. **6** (April) 1873.

[4] Bohn: Das Wechselfieber und seine verschiedenen Formen im Kindesalter, Jahrb. f. Kinderh. **6**: (April) 1873.

[5] Meara, F. S.: A Case of So-Called Congenital Malaria, Arch. Pediat. **26**:517, 1909.

[6] Crandall: New York Polyclin. **1**:38, 1893.

[7] Hitte, L.: Le Paludisme Congenital, Thésé de Montpellier, 1902.

[8] Economo: Bull. de la Soc. d'obst. de Par. **10**:70, 1907.

[9] Bass, Murray H.: Congenital Malaria, Arch. Pediat. **31**:251, 1914.

[10] Lamaire, Dumolard and Laffont: A New Case of Congenital Malaria, Ann. de méd. et chir. enf. **14**:704, 1910.

Concetti[11] believes that a placental infarct is necessary to account for such infection. Thibault[12] examined the blood of 246 new-born infants whose mothers had active malaria, and found that only three of the babies had the parasites in their blood. Some abnormality of gestation or accident of delivery may therefore be safely presumed, since the parasites pass the placental filter so rarely. That active malaria is not necessary in the mother, as most authors have insisted, is shown by the cases of Beekel and by my own case. Kaufman[13] states that pregnancy is apt to bring into activity a latent malarial infection, but in Beekel's case and in my own case, no history of malarial symptoms during pregnancy was obtained from the mothers.

Besides the twenty-eight cases which I have considered conclusive, there have been reported eight cases in which the evidence is strongly in favor of intra-uterine infection. These cases have been reported by Jones;[14] Howard;[15] Josephson;[16] Moncorvo,[17] (three cases); Peters[18] and Mauca.[19] In spite of all the evidence in favor of true congenital malaria, some Italian authors are still skeptical. Sabella,[20] writing in 1911, quotes twenty-six authorities and concludes that congenital malaria does not exist. Mauca reported a probable case in a 27 day old infant, but since it came from a malarial district he doubts its congenital origin, as well as that of other cases reported.

CONCLUSIONS

1. The case here reported owes its chief interest to the fact that the anopheles mosquito can be excluded as the source of infection, and that intra-uterine infection, therefore, does occur.

2. Active malaria in the mother during the latter part of pregnancy is not essential for transmission of the disease to the fetus. In both Beekel's case and in my own the malaria was latent in the mother.

---

[11] Concetti, L.: A Case of Congenital Malaria, La Propaganda Antimalarica Napoli **5**:14, 1912.

[12] Thibault, H.: Congenital Malaria, J. Arkansas M. Soc. **12**:243, 1915.

[13] Kaufman, B.: The Relation of Malaria to Pregnancy, New York M. J. **110**:1028 (Dec.) 1919.

[14] Jones, D. W., and Moore, H. L., in discussion on Smith, M.: Malaria in Infants, South. M. J. **11**:213 (March) 1918.

[15] Howard, W. A.: Letter to Editor, Pediatrics **8**:320, 1899.

[16] Josephson, J. C.: Malaria in a Child of Three Weeks, Med. Rec. **59**: 635, 1901.

[17] Moncorvo: Malaria in Children, Pediatria **8**:95, 143, 191, 239, 1899.

[18] Peters, L.: Malarial Fever in Infancy, Probably Maternal in Origin, Bull. Johns Hopkins Hosp. **13**:139, 1902.

[19] Mauca, M.: A Case of Malaria in the New-Born, of Probably Congenital Origin, Pediatria **22**:598, 1914.

[20] Sabella, Pietro: On Congenital Malaria, Policlinico **18**:145, 1911.

SUMMARY OF THE TWENTY-EIGHT REPORTED CASES

Author	No. of Cases	Age Malaria Discovered in Infant	History of Malaria in Mother During Pregnancy	Plasmodia in Infant's Blood	Plasmodia in Mother's Blood	Remarks
Bohn[4]	1	Premature, dead	....	....	....	Necropsy evidence
Meara[5]	1	7 weeks	yes	yes	yes	
Duschek[3]	1	3 hours	....	....	....	Necropsy evidence
Crandall[6]	1	72 hours	....	yes		
Economo[8]	6	Within 48 hours	yes	yes		
Hitte[7]	2	At birth	....	yes	....	Blood from umbilical cord
Beekel[2]	1	7 weeks	no	yes	no	
Bass[9]	2	7½ weeks and immediately after birth	yes	yes	no yes	
Thibault[12]	4	3 hours	yes	yes		
		2 days	yes	yes	yes	
		5 days	yes	yes	yes	
		Dead at birth	yes	yes	yes	
Jones-Moore[14]	1	9 days	yes	yes		
Rabinoff[21]	1	Few hours	yes	yes		
Lamaire, Dumolard and Laffont[10]	1	Birth	yes	yes	yes	No symptoms till 40 days old
Tissier and Brumpt[22]	1	19 days	yes	yes	yes	
Leger[23]	1	Stillborn 7 months	yes	yes	yes	
Heiser[24]	1	5 days	yes	yes		
Bloom[25]	1	3 weeks	yes	yes	yes	
Caudra[26]	1	2 days	....	yes	yes	
Pennato[27]	1	Born dead	yes	....	....	Necropsy evidence

3. Malaria in the new-born may also be relatively latent but becomes active within a few weeks after birth.

4. Since malaria in pregnant mothers is common, but transplacental infection is quite rare, it is reasonable to presume that congenital malaria may depend on some abnormality of gestation or accident of delivery.

---

21. Rabinoff, Sophie: Some Experiences with Malaria Among Children in Palestine, Arch. Pediat. **37**:494 (Aug.) 1920.

22. Tissier and Brumpt: A Case of Congenital Malaria, Arch. méns. d'obst. et de gynéc. **3**:166, 1913.

23. Leger, M.: Congenital Paludism—a Case of Blood Infection of the Fetus by Plasmodium Vivax, Bull. Soc. de path. exot. **11**:841, 1918.

24. Heiser, V. G.: Malaria in the New-Born, Med. Rec. **84**:855, 1913.

25. Bloom, C. J.: Tertian Malaria in Two Infants Under Two Months of Age, Am. J. Dis. Child. **16**:391 (Nov.) 1918.

26. Caudra: Un cas de paludisme congenital, Arch. de méd. d. enf., 1920.

27. Pennato: Sulla malaria congenita, Riv. crit. di clin. med. **22**:85 (March) 1921.

THE EXCRETION OF FOREIGN PROTEIN IN HUMAN MILK *

HAROLD C. STUART, M.D.
BOSTON

In any series of infantile eczema cases studied by means of the cutaneous reactions to foreign proteins, the most perplexing problem which one encounters is the interpretation of reactions found positive to foods which, as such, have never entered the infant's diet. The frequent finding of a marked egg white reaction in early infancy, demonstrable on repeated applications, often in those exclusively breast fed, is the most notable example. Various explanations have been offered for such sensitizations. The most natural suggestion is that they are inherited, but, as Cooke and Vander Veer [1] have shown, the factor of inheritance seems limited to a tendency to develop sensitizations, a specific sensitization in the descendant rarely being traceable to the antecedents. A temporary transfer by the mother, such as is shown by animals, would not explain the delayed appearance of sensitization so often observed in infants, even if one assumed that the mother had an underlying sensitization which was in a refractory state when under observation. A quite different explanation suggests that the infants in question have become actively sensitized to proteins closely related to the ones giving positive tests, and that, therefore, the latter are evidences of "group" and not specific sensitization. I recently saw a young child who gave positive reactions to several of the nut proteins, although never having eaten nuts. It was later discovered, however, that cocoa also caused a reaction, and cocoa was being taken daily. Undoubtedly a "group" reaction explained the positive reactions to nuts. But in most infants there is no evidence of exposure to any related proteins. There are those also who believe that these skin reactions are not an evidence of sensitization at all, but merely an expression of a peculiar irritability of the skin. For such a theory to explain why some infants will repeatedly give egg white reactions and never respond to casein, while others will reverse this picture, it must presuppose a very specialized idiosyncracy on the part of the skin. This concept holds much in common with that of specific sensitization.

The theory given most credence of late is that these patients become sensitized by the direct transmission of unaltered protein through their

---

* Received for publication, Nov. 10, 1922.

* From the Department of Pediatrics, Harvard Medical School.

1. Cooke, R. A., and Vander Veer, A., Jr.: J. Immunol. **1**:3 (June) 1916.

mothers' milk. Lust,[2] Hayashi,[3] and Schloss and Worthen[4] have shown that under some circumstances an infant will absorb unaltered protein into its blood stream. Assuming that an adult may do the same thing under special conditions, it seems possible that such proteins might enter the breast milk. Clinically one occasionally sees an infant whose skin eruption improves when proteins to which it shows a positive reaction are removed from its mother's diet, but in my experience a striking relationship has been exceptional. In only one of the nine cases reported herewith did the addition or subtraction of these substances from the diet seem to produce corresponding changes in the condition of the skin. Because of such occasional cases, however, I sought to determine whether the presence of egg white protein is demonstrable, by guinea-pig experimentation, in the milk of mothers of infants that are sensitive to egg white, when they take rather large amounts of egg white. The breast milk collected from these mothers was used in an attempt both to sensitize and to shock guinea-pigs. The intravenous and the uterine strip methods were originally employed for the shock injection, it being felt that the latter would be the more satisfactory in providing graphic tracings of results, but the former would be more satisfactory in offering suitable confirmatory evidence, at the same time allowing the use of male pigs.

Shortly after undertaking this work, Shannon[5] published some experiments dealing with the same type of case, but using the intrathecal method of Besredka for his second or shock injection. From his results he concluded that egg protein does appear in the breast milk of mothers under these circumstances. This conclusion was based on tests made on milk collected from three mothers, whose diets contained from one to six eggs daily, the milk being collected from four to twelve hours after the ingestion of the last eggs. Seven guinea-pigs were first sensitized to egg, and after an interval of from twelve to fourteen days they were given an intrathecal injection of one of the breast milk specimens, followed after some time by an intraperitoneal injection of 1 c.c. All these guinea-pigs had marked reactions, and died within twenty-four hours, none, however, within the first few hours. One guinea-pig was sensitized with milk collected about four hours after the mother had eaten two eggs, and it was given a shock injection of egg white intrathecally, the reaction being mild, with complete recovery. As controls one guinea-pig was shocked and one was sensitized with breast milk from one of the mothers after she had been on an egg free diet for two weeks. Six normal guinea-pigs were also given intrathecal injections of the same samples of breast milk as those used in the test guinea-pigs, and no reactions were obtained. Briefly, eight tests guinea-pigs all showed reactions, while eight control guinea-pigs showed no reactions. A few drops of milk from the mother that took only one egg a day (the interval after the taking of this egg not being specified) contained sufficient egg protein to determine a positive reaction. Again, in a later article, Shannon [6] mentions having also demonstrated the presence of veal protein in the milk of mothers whose infants gave a positive veal cutaneous reaction; but none of the details of this work are given.

---

[2] Lust: Jahrb. f. Kinderh. **77**:244, 283, 1913.

[3] Hayashi, J.: Monatschr. f. Kinderh. **12**:749, 1914.

[4] Schloss, O. M., and Worthen, T. W.: Undigested Protein, Am. J. Dis. Child. **11**:342 (April) 1916.

[5] Shannon, W. R.: Demonstration of Food Proteins in Human Breast Milk by Anaphylactic Experiments on Guinea-Pigs, Their Probable Relationship to Certain Diseases of the Nursing Infant, Am. J. Dis. Child. **22**:223 (Sept.) 1921.

Owing to the rather small series presented by Shannon, and because of certain considerations relating to his method which will be discussed later, I determined to continue my work and, if possible, to confirm the findings already published, using methods which I believe to be more suitable for this type of investigation. It seemed to me that if egg protein is demonstrable in breast milk when injected intrathecally, it should also be demonstrable by the intravenous route, or by the uterine strip method. I was particularly anxious to obtain graphic tracings which would eliminate the personal element in the interpretation of mild anaphylactic responses.

REPORT OF CASES

Case 1.—P. Z., aged 3 months, had had eczema since the early weeks of life. The child was breast fed for the first two months, but the eczema had been worse since the addition of one bottle of milk at that time. Skin reactions were positive to both egg white and cow's milk. Both these substances were removed from the mother's diet, after collecting milk for tests, and the infant was given only breast milk. Minute doses of egg white and cow's milk were started by mouth. The skin became clear in three weeks, and the infant was weaned and given Dryco at the end of the course of treatment, without recurrence.

Case 2.—M. G., aged 2 months, had had eczema since the second week of life. The infant had been partly bottle fed and partly breast fed, but gave no reaction to cow's milk protein. Egg white caused a marked cutaneous reaction. Since the mother had very little milk, it was used in experiments directly, without first giving the mother an egg free diet. The baby was completely weaned soon afterward. This was followed by disappearance of the eczema. The eczema returned two months later during the course of oral desensitization to egg white.

Case 3.—E. B., aged 10 months, had eczema of four months' duration. It was a breast fed baby. The reaction to egg white was positive. The mother was given an egg free diet for two weeks. No change in the condition of the infant resulted.

Case 4.—G. C., aged 6 months, was entirely breast fed, but had had eczema since 6 weeks of age. Cutaneous reactions were markedly positive to egg white, lactalbumin, casein, cow's milk and goat's milk. Egg was eliminated, but milk was only reduced in amount, as it was felt to be important to keep the mother's supply of milk up to the infant's requirements. No striking change occurred in the skin manifestations.

---

[6] Shannon, W. R.: Minnesota Med. **5**:137 (March) 1922.

Case 5.—M. C., aged 8 months, was entirely breast fed, but had had eczema since the fourth month. Cutaneous reactions were markedly positive to egg white, and lactalbumin; faintly positive to casein and goat's milk. Milk was collected directly without observing the effect of limiting the mother's diet.

Case 6.—O. P., aged 4 months, had had eczema since the early weeks of life. The egg white reaction was the only one that was positive. The mother was put on an egg free diet for ten days. There was some improvement in the eczema, but it was still quite active at the end of the period, when milk was collected for tests.

Case 7.—This was a patient of Dr. F. S. Churchill of Milton, Mass., tc whom I am indebted for the samples of milk and the information regarding this case. The child was a 6 months' old infant that had showed skin reactions markedly positive to egg white and cow's milk. The eruption cleared rapidly after removal of these foods from the mother's diet. It returned on several occasions on the day following ingestion of egg by the mother.

Case 8.—M. M., aged 8 months, had had eczema of four months' duration. Egg white was the only protein causing a positive reaction. The baby was completely weaned shortly after testing the milk, but the eczema did not clear up for several months on an egg free diet.

Case 9.—J. C., aged 4 months, had had eczema since 5 weeks of age. The child was very much overweight for its age. It showed cutaneous reaction only to egg white. Milk for tests was collected first; the mother was then put on an egg free diet. Very gradual improvement occurred in the skin eruption. (The child was lost sight of before the eczema had completely disappeared.)

PROTOCOLS OF EXPERIMENTS

Experiment 1.—Egg sensitive guinea-pigs were tested with breast milk intravenously. Guinea-pigs were sensitized intraperitoneally with 0.1 c.c. of a one-tenth to one-fiftieth dilution of filtered egg white. The egg white was cut up before making the dilutions, but the ultimate filtering, particularly in the more concentrated dilutions, usually removed some of the egg white. Therefore, the dilution as given in the tables of all the experiments represents a slightly lower concentration than that actually given. The test injection was given at an interval of from three to sixteen weeks after the sensitizing injection, control guinea-pigs being shown to be sensitive at these intervals, and after these doses. Many of the guinea-pigs were given an injection of egg white on the day following the test injection, and all guinea-pigs thus treated died directly in typical anaphylactic shock.

Breast milk from the mothers of five of the nine infants was used in this experiment. Believing that egg protein would be present in the breast milk, in very minute traces, if at all, I attempted to make this concentration as great as possible by collecting the milk at definite intervals after the ingestion of large amounts of egg white. Different intervals were tried, owing to lack of knowledge regarding the time required for such protein to enter the milk. Separate specimens covering various intervals up to nine hours were collected, in some guinea-pigs being used separately, in others several such specimens being mixed. In addition, all but two of the mothers were on a diet containing from two to four cooked eggs a day for some time prior to the tests. These two mothers had been on an egg free diet for from one to two weeks, and a specimen of milk taken before the ingestion of the eggs served as a control in one of them. Milk when collected was skimmed but not heated. Doses ranging from 0.6 to 2 c.c. were injected into the jugular vein, the usual dose being from 1 to 1.5 c.c.

Eleven of the thirteen test guinea-pigs showed absolutely no reaction. The remaining two looked sick for the first one half to two hours, shivering and occasionally showing gross rigor, but these were in no way suggestive of the involuntary twitchings and the bucking movements of true anaphylaxis. No guinea-pigs died as a result of the injection; none showed convulsive movements, and no symptoms were detected which were not detected in control guinea-pigs. Eight normal control guinea-pigs were given from 1 to 2 c.c. of similar samples of breast milk, and two of these shivered and looked sick after injection. Normal guinea-pigs given larger amounts of milk intravenously showed these toxic symptoms so regularly that 2 c.c. was set as the upper limit. The mild reactions to the smaller injections shown by two test and two control guinea-pigs were likewise considered toxic.

Four egg sensitive guinea-pigs were given breast milk, to which small amounts of egg white were added. Three of these guinea-pigs died with typical convulsions within five minutes, while the fourth guinea-pig had severe convulsions but recovered. In Guinea-Pig 191 less than 0.0002 c.c. of egg white added to breast milk caused severe convulsions.

Experiment 2.—Guinea-pigs were injected intraperitoneally or subcutaneously with various samples of breast milk collected from mothers of eight different infants suffering with eczema, from 2 to 7 c.c. being used intraperitoneally, and from 6 to 15 c.c. subcutaneously. In a few cases this milk was heated to 65 C. for twenty minutes before injection, because it was collected outside under unsterile conditions, but usually fresh milk was used lest even this amount of heating might alter the sensitizing power of the protein. The milk was collected at intervals up to twenty hours after the mothers had eaten both raw and cooked eggs. The interval allowed for sensitization ranged from fourteen (in one guinea-pig) to thirty-three days, the second injection being from 0.2 to 1.5 c.c. of a 1:5 or 1:10 dilution of egg white intravenously. Of the twenty-one test guinea-pigs in this series, sixteen showed absolutely no reaction, while the other five showed only the restlessness and shivering noted in some of the seven controls. Five of these were subsequently shown to have been sensitized to breast milk, while the others were not tested in this manner.

In the case of one control guinea-pig egg white was added to the sensitizing injection of breast milk, and the animal died in typical shock when reinjected with egg white.

Experiment 3.—Guinea-pigs were sensitized to egg white intraperitoneally as in Experiment 1. After an interval of three or more weeks (in one case only eleven days) the animals were killed and the uteri set up in apparatus described by Dale.[7]

Virgin guinea-pigs were used, weighing, when killed, from 225 to 375 gm. It was found that breast milk in concentrations of 1:50 or stronger would regularly cause contraction of the uterine strip in control guinea-pigs, but a concentration of 1:100 did not prove toxic (Guinea-Pigs 35, 100, 128, 25, 22, 39). In the tests, therefore, sufficient milk was added to the Ringer's solution to make a final dilution of 1:100 or 1:150. Milk from six mothers was used, the milk having the same relation to the ingestion of eggs as noted in the previous experiments. The milk was used without heating.

The muscle strip was first allowed to become quiet and the kymograph was started to get a quiet base line. Test breast milk, control breast milk and egg white dilutions were then added in various sequences, the reaction to the egg white proving that the guinea-pigs were sensitized. No contraction was produced in any animal by concentrations of test breast milk which did not produce reactions in controls. The curves obtained in two of these guinea-pigs are given. This experiment, however, was not found to be so satisfactory as the reverse procedure described under Experiment 4, because of the toxic action of breast milk on the uterus, when present in high concentration.

---

[7] Dale, H. H.: J. Pharmacol. & Exper. Therap. **4**:167, 1912.

Experiment 4. — Guinea-pigs were sensitized with the breast milk either subcutaneously or intraperitoneally, and, after an interval of from eighteen to thirty-three days, were killed and the uteri set up in the Dale apparatus. This experiment was found to be the most satisfactory of all because it permitted the use of the test material for sensitizing, which is known to require a smaller dose than shocking; and further egg white in concentrations of 1:250 in Ringer's solution caused no irritation of normal muscle, whereas 1:50,000 would cause marked contractions in sensitized uteri. Tracings were taken of eleven test

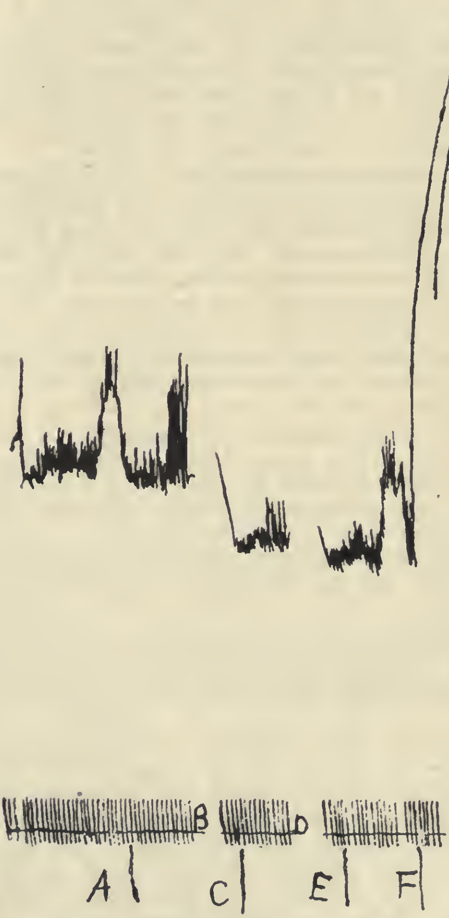


Fig. 1 (Experiment 3, Case 8, Guinea-Pig 171, weight, 250 gm.).—Tracing made eleven days after the guinea-pig had been given 0.1 c.c. of a 1:50 dilution of egg white intraperitoneally: *A,* results following application of breast milk, collected three hours after the mothers had eaten the last two eggs (cooked) in the diet, to which had been added sufficient Ringer's solution to make a 1:150 concentration; *C,* results following the application of breast milk in the same concentration, collected six hours after the ingestion of eggs; *E,* results following the application of breast milk collected nine hours after the ingestion of eggs; *F,* effect of application of an egg white dilution added in a concentration of 1:500. The resulting contraction was immediate and complete. In this illustration and in Figures 2 and 4, time markings are in minutes, and breaks in the line indicate changes of Ringer's solution.

guinea-pigs (i. e., guinea-pigs sensitized with test breast milk), and not one of these showed any reaction to egg white, but all gave typical anaphylactic curves when breast milk was added. Normal guinea-pigs and guinea-pigs sensitized to egg white were both used as controls. Two of the tracings of the test guinea-pigs are given.

An analysis of these protocols and the accompanying tables reveals not the slightest suggestion of anaphylactic reactions in any of the test guinea-pigs. We had looked more hopefully to Experiments 2 and 4, those in which the breast milk had been used to sensitize, because much larger amounts of milk could be used for this purpose, and it is known that smaller amounts are required to sensitize than to shock.

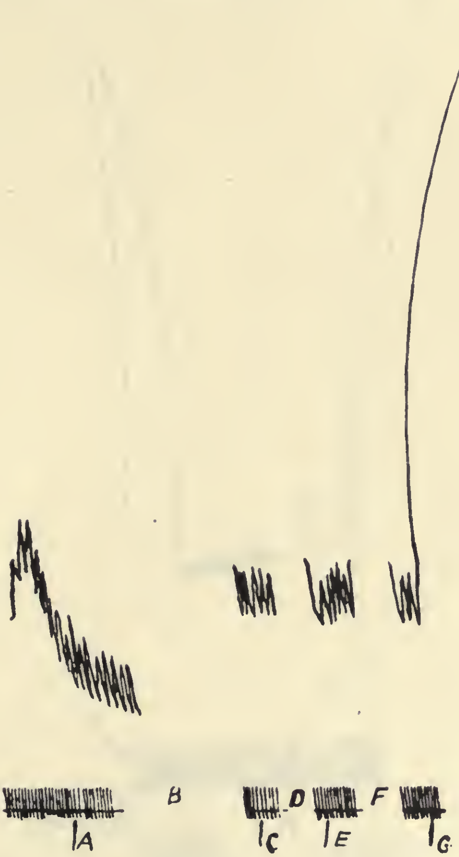


Fig. 2 (Experiment 3, Case 8, Guinea-Pig 126, weight, 300 gm.).—Tracings made thirty-five days after guinea-pig had been sensitized with 0.1 c.c. of a 1:10 dilution of egg white intraperitoneally: *A*, results of application of breast milk collected three hours after the ingestion of eggs; *C*, results following the application of breast milk collected six hours after the ingestion of eggs; *E*, results following the application of breast milk collected nine hours after the ingestion of eggs; *G*, results following the application of egg white in concentration of 1:150, causing immediate complete contraction.

These experiments did prove to be the most satisfactory because breast milk occasionally produced mild toxic symptoms when introduced intravenously and when added to the uterine strip, both in tests and in controls; whereas egg white proved to be nontoxic in very large doses. But the tables show that as much as 15 c.c. of breast milk collected after the ingestion of large quantities of egg failed to sensitize. It occurred to me that the great preponderance of breast milk protein in the test material might in some way inhibit the action of the egg protein, so a number of control guinea-pigs were injected with breast milk containing a very small amount of added egg white, as shown in the tables. These injections were capable of shocking sensitive guinea-pigs and

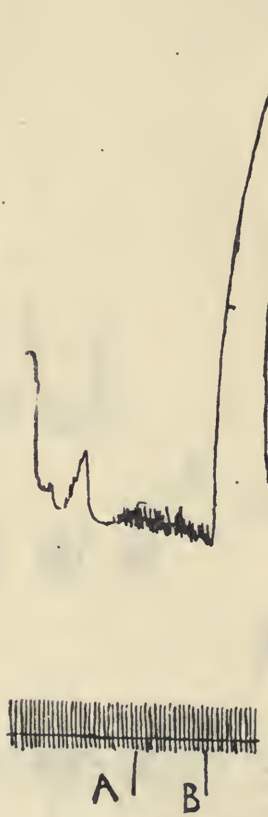


Fig. 3 (Experiment 4, Case 8, Guinea-Pig 199, weight, 270 gm.).—Tracings taken three weeks after guinea-pig had been sensitized with 5 c.c. of milk collected after six hours, subcutaneously: *A,* results after application of egg white in concentration of 1:500; *B,* results following the application of mixed sample of breast milk in concentration of 1:200. Contraction was complete. The time tracings are in minutes.

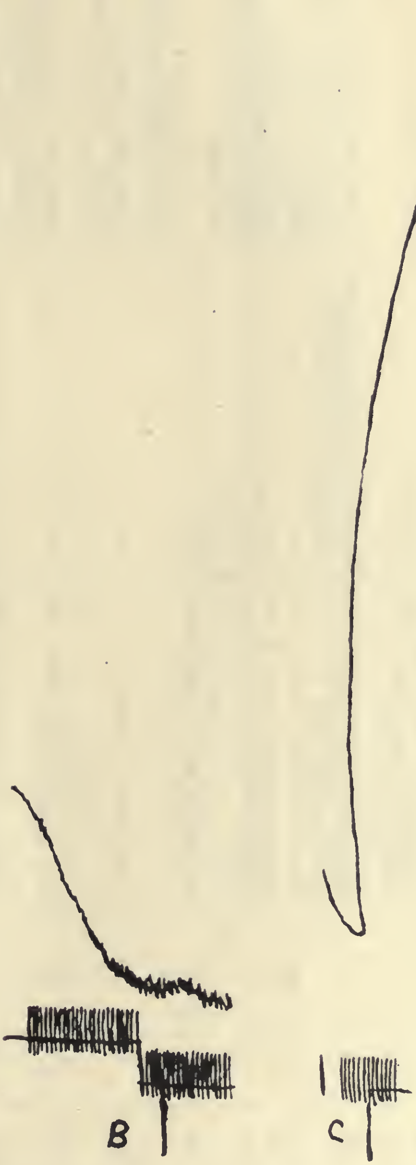


Fig. 4 (Experiment 4, Case 8, Guinea-Pig 200, weight, 225 gm.).—Tracings made eighteen days after guinea-pig had been sensitized with 5 c.c. of mixed nursings from a mother taking four cooked eggs a day: *B,* results following the application of Ringer's solution to which had been added egg white in a dilution of 1:1,000; *C,* results following the application of a mixed sample of breast milk added in a concentration of 1:200. Immediate complete contraction resulted.

TABLE 1 (Experiment 1).—Guinea-Pigs Sensitized with Egg White Intraperitoneally: Subsequent Injection with Skimmed Fresh Breast Milk Intravenously

Case	Guinea-Pig	Amount Egg White Dilution, C.c.	Dilution Egg White	Interval Between Injections, Days	Amount Second Injection Breast Milk, C.c.	Description of Milk Used, i. e., Relation to Egg in Diet Form in Which Eggs Taken	Reaction	Subsequent Injections or Necropsy Findings
1	12	0.4	1:40	57	1.5	Mother eating 2 eggs twice daily (cooked). Mixed of 3 nursings	None	
2	2	0.4	1:40	110	0.6	Four raw whites given in milk. Milk collected 3, 6 and 9 hours after, mixed in equal parts	None..............................	Necropsy negative
3	10	0.4	1:40	110	1.5	Four raw whites given in milk. Milk collected 3, 6 and 9 hours after, mixed in equal parts	Shivered and showed gross rigors first hour. Looked sick rest of afternoon. Normal next day	24 hours later given 0.1 c.c. of 1:5 egg white intravenously. Died in 3 min. in convulsions. Necropsy negative
4	16	0.5	1:25	63	1.5	Four raw egg whites given in milk. Specimen collected 2 hours later	None..............................	24 hours later given 0.1 c.c. of 1:5 egg white dilution intravenously. Guinea-pig died in convulsions in a few minutes
4	30	0.3	1:10	27	1.5	Four raw egg whites. Milk collected 5 and 8 hours after (mixed)	None..............................	24 hours later given 0.5 c.c. of 1:5 egg white dilution intravenously. Died in 10 minutes with convulsions
4 Control	28	0.3	1:10	28	1.5	On egg-free diet 2 weeks.............	None..............................	24 hours later given 0.1 c.c. of 1:5 egg white. Died in 10 minutes with convulsions
8	121	0.1	1:10	34	1.5	Eating 4 cooked eggs daily. Milk of 3 nursings mixed	None..............................	Following day given 0.3 c.c. of 1:10 egg white intravenously. Died with convulsions in 3 minutes
9	127	0.1	1:10	34	1.5	Eating 4 cooked eggs daily. Milk collected 3 hours after last eggs	Shivered violently first half hour. Otherwise normal	Killed in 2 minutes following day by injection of 0.3 c.c. of 1:10 egg white
8 Control	195a*	...	....	...	...	Same as Guinea-Pig 127..............	Scratched nose violently several times. Shivered first hour	
9	188	0.1	1:10	66	1.0	Taking 4 cooked eggs daily. Milk collected 2 (also 6) hours after last eggs	None..............................	24 hours later given 0.1 c.c. of 1:5 egg white intravenously. Died in 3 minutes in convulsions

9	189	0.1	1:10	66	1.25	Taking 4 cooked eggs daily. Milk collected 2 (also 6) hours after last eggs	None	
9	185	0.1	1:10	66	1.5			
9	186	0.1	1:10	66	1.0			
9	187	0.1	1:10	66	1.0			
9	212	0.1	1:10	48	1.5			
Control	231*	...	....	...	1.5			
Control	237*	...	....	...	1.5			
Control	240*	...	....	...	1.5			
Control	241*	...	....	...	1.0			
Control	164*	...	....	...	1.5			
Control	166*	...	....	...	1.5			
Control	167*	...	....	...	2.0	Taking 4 cooked eggs daily. Milk collected 2 (also 6) hours after last eggs	Shivered and hair puffed out 15 minutes	
Control	118	0.1	1:10	58	1.5	Mother of normal infant, eating eggs twice daily	Shivered few minutes and looked sick 2 hours. Then normal	Following day given 0.5 c.c. of 1:10 egg white intravenously. Died in convulsions in 3 minutes
Control	150	0.1	1:10	20	2.0	Mother of normal infant, eating eggs twice daily	None..............................	Injected like Guinea-Pig 118, and died in typical convulsions in 2 minutes
Control	184	0.1	1:10	66	1.0	Milk of Case 10 containing 0.1 c.c. of 1:10 egg white	Died in typical convulsions in 5 minutes	
Control	204	0.1	1:50	66	1.0	Milk of Case 10 containing 0.1 c.c. of 1:10 egg white	Died in typical convulsions in 5 minutes	
Control	207	0.1	1:50	66	0.05	Milk of Case 10 containing 0.005 c.c. of 1:10 egg white	Died in typical convulsions in 2 minutes	
Control	191	0.1	1:10	66	0.02	Milk of Case 10 containing 0.002 c.c. of 1:10 egg white	In 3 minutes sneezing, scratching, defecating. In 5 minutes on side in severe convulsions. In 10 minutes on feet again but convulsing. In 15 minutes quiet. Recovered	
Control	213	0.1	1:10	50	0.1	Of 1:1,000 dilution egg white..........	Died in 3 minutes with typical convulsions	

---

* Normal guinea-pig.

TABLE 2 (EXPERIMENT 2).—GUINEA-PIG SENSITIZED WITH BREAST MILK: SUBSEQUENT INJECTION WITH EGG WHITE INTRAVENOUSLY

Case	Guinea-Pig	Route of First Injection	Amount Breast Milk First Injection, C.c.	Description of Milk Used, i. e., Relation to Egg in Diet. Form in Which Eggs Taken Treatment of Milk	Interval Between Injections, Days	Amount Egg White Second Injection, C.c.	Dilution of Egg White	Reaction	Subsequent Injections and Necropsy Findings
1	19	Intraperitoneal	2	Taking 2 cooked eggs twice daily. Mixed 3 nursings. Milk not heated	33	0.3	1:5	No reaction......................	After 24 hrs. given 0.3 c.c. breast milk. Died in 10 min. in typical convulsions
2	20	Intraperitoneal	2	Taking 2 cooked eggs twice daily. Mixed 3 nursings. Milk not heated	33	0.3	1:5	No reaction......................	Given 0.15 c.c. breast milk intravenously next day. Mild convulsion, definite anaphylaxis but recovery
4	59	Intraperitoneal	2	Mother given whites of 4 raw eggs in milk. Two, five and eight hrs. after specimens mixed. Milk not heated	15	0.8	1:5	Shivered constantly 45 min. looking sick and irritable. No convulsive movements, hair not on end, no sneezing, urinating, or defecating	
5	69	Subcutaneous	6	Two hours, after 4 raw eggs. Milk pasteurized	24	0.2	1:5	No reaction......................	Necropsy showed pneumonia
5	70	Subcutaneous	6	Five hours, after 4 raw eggs. Milk pasteurized	24	0.2	1:5	Restless few minutes, then normal	Necropsy negative
5	83	Intraperitoneal	6	Two hours, after 4 raw eggs. Milk not heated	25	1.5	1:5	No reaction......................	After 2 days given 0.07 c.c. breast milk intrathecally. Def. reaction but recovered
5	93	Subcutaneous	11	Two hours, after 4 raw eggs. Milk pasteurized	23	1.0	1:5	No reaction	
5	94	Subcutaneous	6	Five hours, after 4 raw eggs. Milk not heated	23	1.5	1:5	Looked sick for 5 min. but normal thereafter	
5	96	Intraperitoneal	6	Five hours, after 4 raw eggs. Milk pasteurized.	25	1.0	1:5	No reaction	
5	114	Subcutaneous	8	Two hours, after 4 raw eggs. Milk pasteurized	23	1.0	1:10	No reaction	
5	115	Subcutaneous	8	Five hours, after 4 raw eggs. Milk pasteurized	23	1.0	1:10	No reaction	
6	72	Subcutaneous	15	Five hours, after 4 raw eggs. Milk pasteurized	33	0.6	1:5	No reaction	

7	82	Subcutaneous	10	Twenty hours, after 4 raw eggs. Milk not heated	17	1.0	1:5	Shivered, breathed fast and looked sick 2 hrs., then normal	After 2 days given 0.1 c.c. breast milk intrathecally. Def. reaction, but recovered
7	142	Subcutaneous	3	Eight hours, after 4 raw eggs. Milk not heated	14	1.0	1:5	No reaction......................	Next day given 0.07 c.c. boiled breast milk intrathecally. Severe convulsions with recovery
7 Control	143	Intraperitoneal	5	Eight hours, milk containing 0.1 of 1:10 egg white	17	1.0	1:5	Violent spasms, involuntary urination and death in 3 minutes	Necropsy showed distended lungs
8	196	Intraperitoneal	3	Two cooked eggs twice daily. Milk from 3 mixed nursings. Not heated	21	0.3	1:5	No reaction	
8	197	Subcutaneous	6	Two cooked eggs twice daily. Milk from 3 mixed nursings. Not heated	21	0.3	1:5	Shivered and gross rigors, irritable, and looked sick up to 2 hours	
8	197a	Intraperitoneal	5	Two cooked eggs twice daily. Milk from 3 mixed nursings. Not heated	21	0.5	1:5	No reaction	
9	232	Intraperitoneal	7	Four cooked eggs daily. 3½ (also 6½) hours, after 2 eggs. Milk not heated	21	0.5	1:10	No reaction	
9	233	Intraperitoneal	5	Four cooked eggs daily. 3½ (also 6½) hours, after 2 eggs. Milk not heated	21	0.5	1:10	No reaction	
9	234	Intraperitoneal	5	Four cooked eggs daily. 3½ (also 6½) hours, after 2 eggs. Milk not heated	21	0.5	1:10	No reaction	
9	235	Intraperitoneal	5	Four cooked eggs daily. 3½ (also 6½) hours, after 2 eggs. Milk not heated	21	0.5	1:10	No reaction	
Control	213	Intraperitoneal	0.1	1:10 dilution of egg white.........	50	0.1	1:1000	Died in 3 minutes with typical convulsions	
Control	218	....	....	Normal guinea-pig	..	0.3	1:5	No reaction	
Control	219	....	....	Normal guinea-pig	..	0.5	1:5	Slight shivering, then normal	
Control	165	....	....	Normal guinea-pig	..	1.5	1:10	No reaction......................	Necropsy negative
Control	168	....	....	Normal guinea-pig	.	1.5	1:5	Marked rigors first few minutes, then normal	Necropsy negative
Control	180	....	....	Normal guinea-pig	..	0.5	1:5	First 15 minutes looked irritable, breathed fast, scratched nose; then quiet and normal	Necropsy negative
Control	181	....	....	Normal guinea-pig	..	1.5	1:5	Shivered constantly, hair on end, few gross rigors, quiet in corner up to 2 hours	Necropsy negative
Control	182	....	....	Normal guinea-pig	..	1.0	1:5	No reaction, except excited and shivering	Necropsy negative

TABLE 3 (EXPERIMENT 3).—GUINEA-PIGS SENSITIZED WITH EGG WHITE INTRAPERITONEALLY: SUBSEQUENTLY KILLED AND REACTION OF UTERINE STRIP TO TEST BREAST MILK NOTED

Case	Guinea-Pig	Amount Sensitizing Dose Egg White Dilution	Dilution Egg White	Interval Before Killing Guinea-Pig	Number of Test Substances Added in Order	Description of Milk Used, i. e., Relation to Egg in Diet, Form in Which Eggs Taken, Treatment of Milk	Final Dilution of Substances Added to Ringer's Solution	Anaphylactic Response Shown by Immediate Contraction
4	32	0.3	1:10	28	(1)	Breast milk while on egg-free diet........................	1:100	None
					(2)	Breast milk 2 hours after four egg whites..............	1:100	None
6	41	0.1	1:5	53	(1)	Breast milk after egg-free diet..........................	1:100	None
					(2)	Breast milk 2 hours after four egg whites..............	1:100	None
					(3)	Breast milk 5 hours after four egg whites..............	1:100	None
					(4)	Breast milk 5 hours after four egg whites (pasteurized)	1:100	None
8	67	0.1	1:10	34	(1)	Two cooked eggs night and morning. Milk taken 3 hours after eggs	1:100	None
					(2)	Same as (1) repeated..................................	1:100	None
					(3)	Egg white	1:500	Marked
8	171	0.1	1:50	11	(1)	Taking two cooked eggs night and morning. Milk 3 hours after eggs	1:150	None
					(2)	Same, 6 hours after....................................	1:150	None
					(3)	Same, 9 hours after....................................	1:150	None
					(4)	Egg white	1:500	Marked
8	126	0 1	1:10	25	(1)	Taking two cooked eggs night and morning. Milk 3 hours after eggs	1:150	None
					(2)	Same, taken 6 hours after..............................	1:150	None
					(3)	Same, taken 9 hours after..............................	1:150	None
					(4)	Egg white	1:500	Marked
Control	6	0.4	1:40	93	...	Egg white	1:100	Marked
Control	27	0.2	1:10	19	(1)	Egg white	1:1,000	Marked
					(2)	Egg white	1:10,000	Very slight
Control	101	0.1	1:10	28	(1)	Egg white	1:1,000	Complete
					(2)	Breast milk (hospital supply)..........................	1:100	None
					(3)	Egg white	1:1,000	None
					(4)	Egg white	1:1,000	None
Control	103 rt. 103 lft.	0.1	1:10	29	(1)	Egg white	1:1,000	Complete
					(2)	Breast milk (hospital supply)..........................	1:100	None
					(3)	Breast milk (hospital supply)..........................	1:100	None
					(4)	Egg white	1:500	Marked
Control	35*	...	....	..	(1)	Breast milk (hospital supply)..........................	1:50	Slight
					(2)	Egg white	1:100	Marked
					(3)	Breast milk 1:50, containing egg white.................	1:500	Marked
Control	100*	...	....	..	(1)	Breast milk 2 hours after egg white....................	1:50	Moderate
					(2)	Breast milk 5 hours after four egg whites..............	1:50	Moderate
Control	128*	...	....	..	(1)	Egg white	1:250	None
					(2)	Breast milk (hospital supply)..........................	1:100	None
Control	22	2.0	1:10	24	(1)	Egg white	1:50,000	Marked
					(2)	Egg white	1:100,000	Very slight

* Not sensitized.

TABLE 4 (EXPERIMENT 4).—GUINEA-PIGS SENSITIZED WITH TEST BREAST MILK: SUBSEQUENTLY KILLED AND REACTION OF UTERINE STRIP TO EGG WHITE NOTED

Case	Guinea-Pig	Route of Sensitization	Amount of Breast Milk	Description of Milk Used, i. e. Relation to Egg in Diet, Form in Which Egg Taken, Treatment of Milk	Interval Before Killing Guinea-Pig, Days	Number of Tests, in Order	Test Substance Added	Final Dilution in Ringer's Solution	Anaphylactic Response Shown by Immediate Contraction
5	104	Subcutaneous	4	Milk collected 2 hours after whites of four raw eggs. Not heated	33	(1)	Egg white	1:500	None
						(2)	Breast milk	1:100	Complete
5	107	Intraperitoneal	4	Milk collected 5 hours after four egg whites (raw). Milk heated to 65 for 20 minutes	33	(1)	Egg white	1:250	None
						(2)	Breast milk	1:500	Marked
5	120	Subcutaneous	6	Milk collected 5 hours after four egg whites (raw). Milk heated to 65 for 20 minutes	23	(1)	Egg white	1:1000	None
						(2)	Breast milk	1:100	Complete
5	105	Subcutaneous	4	Milk collected 5 hours after four raw egg whites. Milk not heated	33	(1)	Egg white	1:250	None
						(2)	Breast milk	1:250	Complete
6	106	Subcutaneous	10	Mother eating two to four cooked eggs a day. Milk not heated	21	(1)	Egg white	1:250	None
						(2)	Breast milk	1:500	Marked
7	130	Intraperitoneal	6	Milk collected 8 hours after four raw egg whites. Not heated	17	(1)	Egg white	1:250	None
						(2)	Boiled breast milk	1:100	Complete
7	132	Subcutaneous	8	Milk collected 20 hours after four raw egg whites	20	(1)	Egg white	1:200	None
						(2)	Breast milk	1:100	Complete
7	81	Subcutaneous	15	Milk collected 4 hours after eating four egg whites	22	(1)	Egg white	1:100	None
						(2)	Breast milk	1:250	Moderate
7 Control	125	Subcutaneous	8	Breast milk containing 0.1 c.c. of 1:10 egg white	18	(1)	Egg white	1:250	Moderate
						(2)	Breast milk	1:250	Complete
8	200	Subcutaneous	5	Three nursings mixed while on diet of two cooked eggs night and morning. Not heated	18	(1)	Egg white	1:1000	None
						(2)	Breast milk	1:200	Complete
8	198	Subcutaneous	5	Milk collected 3 hours after two cooked eggs. Taking four cooked eggs a day	21	Rt. horn (1)	Egg white	1:500	None
						(2)	Breast milk	1:200	Marked
						Lt. horn (1)	Egg white	1:500	None
						(2)	Breast milk	1:200	Complete
8	199	Subcutaneous	6	Taking two cooked eggs night and two morning. Milk collected 6 hours after last	21	(1)	Egg white	1:500	None
						(2)	Breast milk	1:200	Marked
Control	205†	....	..	....	18	(1)	Egg white	1:1000	Complete
Control	217	....	..	Not sensitized	..	...	Breast milk	1:200	None

† Sensitized with 0.1 c.c. of 1:50 dilution egg white intraperitoneally.
For further controls see Experiment 3.

TABLE 5 (EXPERIMENT 5).—GUINEA-PIGS SENSITIZED WITH EGG WHITE: SUBSEQUENT INJECTION WITH BREAST MILK INTRATHECALLY, METHOD OF GAY AND SOUTHARD USED IN GUINEA-PIGS MARKED G. AND S.; OF BESREDKA IN THOSE MARKED BESR.

Case	Guinea-Pig	Amount of Egg White Dilution, C.c.	Dilution of Egg White	Interval Between Injections, Days	Amount Second Injection Breast Milk, C.c.	Description of Milk Used, i. e., Relation to Egg in Diet, Form in Which Eggs Taken, Treatment of Milk	Reaction	Subsequent Injections or Necropsy Findings
9	211	0.1	1:10	50	0.2 G and S	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	Unconscious 2 min., then up and quiet, looking sick. No spasms. Recovered	Died in typical convulsions following day after 0.1 c.c. of 1:10 egg white intravenously
9	145	0.1	1:10	50	0.1 Besr.	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	No reaction	
9	202	0.1	1:50	66	0.2 Besr.	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	Irritable and sick, scratching head and holding it on side 2 hours. Recovered	
9	176	0.1	1:10	66	0.1 Besr.	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	No reaction	
9	177	0.1	1:10	66	0.2 Besr.	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	Irritable, scratched head and sneezed ½ hour. Later nasal discharge and obstruction. Recovered	
9	175	0.1	1:10	66	0.1 Besr.	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	No reaction	
9	183	0.1	1:10	66	0.1 Besr.	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	No reaction	
9	178	0.1	1:10	66	0.1 Besr.	Mother taking two cooked eggs twice daily. Milk collected sterile 3½ hrs. after last eggs. Not heated	Restless ½ hour. Otherwise negative	
Control	213	0.1	1:10	50	Besr.	Second injection 0.1 c.c. of 1:1000 dilution of egg white	Looked little sick, shivered and occasionally scratched head	24 hours later given 0.5 c.c. of 1:10 egg white intravenously. Died in 3 min. in typical convulsions
Control	203	0.1	1:50	66	Besr.	Second injection 0.15 c.c. of 1:10 egg white dilution	Died in 7 minutes with typical convulsions	
Control	108	0.1	1:10	42	G and S	Second injection 0.1 c.c. of 1:5 egg white	Died in 6 minutes with typical convulsions	

Control	119	0.1	1:10	50	G and S	Second injection 0.05 c.c. of whole egg white	Died in 7 minutes with typical convulsions	
Control	179	0.1	1:10	66	0.05 Besr.	Same as in Case 9 tests but with 0.05 of 1:10 c.c. egg white added	Died in 2 minutes with typical convulsions	
Control	190	0.1	1:10	66	0.01 Besr.	Same as in Case 9 tests but containing 0.01 c.c. of 1:10 egg white	Died in 5 minutes with typical anaphylaxis	
Control	238*	...	....	..	0.01 Besr.	Milk of Case 9......................	Quiet, looked sick, held head to side. Otherwise negative	
Control	239*	...	....	..	0.1 Besr.	Milk of Case 9......................	No reaction	
Control	208*	...	....	..	0.25 Besr.	Mixed specimen of three feedings of another case on four eggs a day diet	In severe pain, crying, lying on side, very irritable 1½ hrs. Recovered	
Control	209*	...	....	..	0.25 Besr.	Mixed specimen of three feedings of another case on four eggs a day diet	Shivered, scratched head, cried, held head on side 2 hours	
Control	155*	...	....	..	0.1 G and S	Hospital mixed sample. This had been boiled	Very sick, after 5 minutes turned many circles to left. Then alternated periods of lying on side, breathing fast, and up about, restless and in pain. At times spasmodic contractures and true convulsions. Quiet after 4 hours	48 hours later, looking normal. Given 0.1 c.c. of egg white above opposite eye, intrathecally. Restless and irritable but otherwise negative
Control	156*	...	....	..	0.1 G and S	Hospital mixed sample. This had been boiled	Fairly well first 2 hours, then very sick with frequent convulsions for 2 hours	48 hours later, looking normal. Given 0.05 c.c. egg white intrathecally. No reaction
Control	157*	...	....	..	0.1 G and S	Hospital mixed sample. This had been boiled	Only held head on side first 1½ hours. Then fell over, convulsed, breathed deep. Soon up again, trying to walk, but again fell over. This lasted several hours	24 hours later, looking normal. Given 0.2 c.c. egg white. Immediately rolled sideways and acted much as day before. Recovered
Control	158*	...	....	..	0.2 G and S	Hospital mixed sample. This had been boiled	Looked sick 1 hour, then normal...	Following day given 0.2 c.c. egg white. Looked sick 1 hour, but recovered
Control	159*	...	....	..	0.3 G and S	Hospital mixed sample. This had been boiled	Made several revolutions, then looked sick 2 hours, then normal	Following day given 0.3 c.c. egg white intrathecally. Looked sick, otherwise negative
Control	153*	...	....	..	0.1 G and S	Hospital mixed sample. This had been boiled	Reacted just as Guinea-Pig 155	
Control	154*	...	....	..	0.1 G and S	Hospital mixed sample. This had been boiled	Reacted just as Guinea-Pig 157	

* Normal guinea-pig.

TABLE 6 (Experiment 6).—Guinea-Pigs Sensitized with Breast Milk: Subsequent Injection with Egg White Intrathecally, Method of Gay and Southard Used in Guinea-Pigs Marked G. and S.; of Besredka in Those Marked Besr.

Case	Guinea-Pig	Route of First Injection	Amount of Breast Milk Sensitizing Injection, C.c.	Description of Milk Used, i. e., Relationship to Egg in Diet Form in Which Eggs Taken. Treatment of Milk	Interval Between Injections, Days	Amount of Second Injection Egg White, C.c.	Dilution of Second Injection in Saline	Reaction	Subsequent Injections or Necropsy Findings
5	65	Intraperitoneal	4	Mother given white of 4 eggs. Milk collected after 2 hours. Milk heated to 65 for 20 min.	37	0.1 G & S	1:5	First hour looked sick and shivered frequently. Next hour held head on side, otherwise well	24 hours later given 0.1 c.c. breast milk intrathecally. Again only looked sick. Necropsy negative except for openings through orbit
5	68	Subcutaneous	6	Mother given white of 4 eggs. Milk collected after 2 hours. Milk heated to 65 for 20 min.	41	0.1 G & S	Whole egg white	Irritable first five minutes, then normal. No twitchings	24 hours later given 0.4 c.c. breast milk intravenously. Died in 4 minutes with convulsion. Necropsy showed lungs distended and opening above orbit
5	85	Subcutaneous	8	Mother given white of 4 eggs. Milk collected after 2 hours. Milk heated to 65 for 20 min.	36	0.05 G & S	Whole egg white	No reaction	48 hours later given 0.07 c.c. breast milk intrathecally. Severe convulsions, but recovery. Necropsy showed both openings into cranium
5	92	Subcutaneous	8	Same as above except milk collected 5 hours after egg	35	0.05 G & S	1:5	Looked sick and shivered. At end of ½ hour, temp. 104 F. Quiet in 4 hours. Dead next forenoon. No convulsions, no paralysis	Necropsy showed hemorrhage about opening above orbit
5 Control	90	Subcutaneous	8	Milk on egg-free diet. Milk not pasteurized	33	0.07 G & S	Whole egg white	No reaction	24 hours later given 1 c.c. of pasteurized milk intravenously. Had typical convulsions but recovered. Necropsy only showed opening into cranium
7	133	Subcutaneous	8	Mother given whites of 4 raw eggs. Four hours later milk collected. Not heated	17	0.1 G & S	Whole egg white	Ran about in circles, violently, 5 minutes; then quiet, but shivering and scratching head occasionally. After 2 hours persisted in holding head on side. Well next day	24 hours later given 0.5 c.c. boiled breast milk intravenously. Died in typical convulsions. Lungs distended. Opening into cranium seen
7 Control	144	Intraperitoneal	8 (containing 0.1 c.c. of 1:10 egg white)	Mother given whites of 4 raw eggs. Four hours later milk collected. Not heated	17	0.1 G & S	Whole egg white	After 10 minutes fell on side, breathing fast, and extremities in spasms. Quieted down after 25 minutes, but looked sick 2½ hours. Scratched nose violently, sneezed often	24 hours later given 0.1 c.c. of breast milk intrathecally. Fell on side and had severe convulsions for 20 minutes. Recovered. Necropsy showed only two openings into cranium

Control	134*	....	...	....	..	0.1 G & S	Whole egg white	Looked sick, held head on side. Otherwise no reaction	Necropsy showed opening into cranium
Control	153*	....	...	....	..	0.1 G & S	Whole egg white	No reaction	Necropsy showed opening into cranium
Control	154*	....	...	....	..	0.1 G & S	Whole egg white	No reaction	Necropsy showed opening into cranium
8	201	Subcutaneous	5	Mother eating 2 cooked eggs twice daily. Milk of mixed 3 feedings after last eggs, i. e., 3, 6 and 4 hours	24	0.25 Besr.	Whole egg white	Unconscious 5 minutes, then made several revolutions and sat quietly for a time, looking sick	Necropsy negative except for perforation through skull
Control	220*	....	...	....	..	0.25 Besr.	Whole egg white	Looked sick, but no reaction	
Control	221*	....	...	....	..	0.25 Besr.	Whole egg white	Very excited, running about cage, evidently in pain. No convulsion, but frequently twitched body	
Control	195*	....	...	....	..	0.25 Besr.	Whole egg white	Very excited 5 minutes, then quiet. After ½ hour, started shivering and crying and working back extremities. Evidently in pain	
Control	203†	....	...	....	59	0.15 Besr.	1:10 egg white	In 3 minutes started deep breathing, in 5 minutes convulsions, and in 7 minutes died	Necropsy showed much distended lungs
Control	108‡	....	...	....	42	0.1 Besr.	1:5 egg white	Died in 6 minutes with typical convulsions	Necropsy showed lungs distended. Opening in cranium
Control	119‡	....	...	....	50	0.05 Besr.	Whole egg white	Died in 7 minutes with typical convulsions	Lungs distended. Opening in cranium

* Normal guinea-pig.

† Guinea-pig sensitized with 0.1 c.c. of 1:50 egg white solution, intraperitoneally.

‡ Sensitized with 0.1 c.c. of 1:10 egg white, intraperitoneally.

sensitizing normal guinea-pigs, so that the presence of breast milk did not inhibit, more than quantitatively at least, the action of the egg white.

The results of the foregoing experiments seemed especially strange when it is considered that Shannon had not only sensitized but had even shocked with much smaller doses and after much less egg; so it was determined to use another series, using the intrathecal route as he had done.

Experiment 5.—In this experiment egg sensitive guinea-pigs were tested with breast milk from Case 10 administered intrathecally. Seven of the injections were made through the vault of the skull, as originally advocated by Besredka,[8] one through the orbit, as suggested by Gay and Southard.[9] Some of these guinea-pigs showed absolutely no reactions, while others were very sick. Eleven normal controls were also used, and a number of these were very sick for some hours, in a few the symptoms being very violent. None of the symptoms in either case suggested anaphylaxis as it appeared in the six egg sensitive guinea-pigs given egg injections, but they sufficiently confused the picture to make the method absolutely unsuitable for milk injections.

Experiment 6.—Guinea-pigs were sensitized with breast milk as for Experiment 4, specimens from three different cases being used. Egg white was given through the orbit in five of these guinea-pigs, and by Besredka's original route in one. Eleven control guinea-pigs were also injected. The details of the reactions are given in the tables. The results are seen to be just as unsatisfactory as those obtained in Experiment 5, and the tests in no way suggest anaphylaxis.

Besredka advocated the intrathecal method because he believed that the anaphylactic reaction was due to a lesion produced by the sensitizing injection in the nervous system, but latent until the administration of the shock dose. By introducing the antigen into direct contact with the central nervous system he hoped to obtain maximum manifestations, and therefore, to be able to detect more minute quantities of antigen in an unknown specimen. This theory, however, has long since been abandoned, the work of Dale [7] and others having shown that the reaction is a local cellular one in the various tissues, independent of central nervous control. Furthermore, the method of Besredka was found to be less reliable than other methods because of the small dose permissable and the false reactions frequently produced by nonspecific central irritation. Gay and Southard [9] used the modification referred to above, which they believed permitted the introduction of larger doses, but since their time very little work has been done by experimenters with the intrathecal route. Pfeiffer,[10] in describing the methods used in anaphylactic investigation, only mentions the intrathecal route as one formerly used but employed very little in recent years. Furthermore, Besredka[11] himself states that the intravenous route is the most effective of all, and advocates only the subdural when using certain substances. He specifically warns against the injection of milk intrathecally unless heated to 100 C. because he has frequently seen guinea-pigs die within twenty-four hours after injections, independently of their anaphylactic state. It is to be noted that all of Shannon's guinea-pigs died after several hours. In our experience death in known anaphylaxis usually occurs within the first one-half hour, or recovery is complete. This fact in itself would render the route unsuitable for one half of Shannon's experiments, that is, shocking egg sensitive guinea-pigs with breast milk; for the milk as used by him had not been subjected to heat. In the other half of his experiments, in which an attempt was made to sensitize guinea-pigs to egg white by injection of breast milk, there is no indication for the use of this method, for properly prepared filtered dilutions of egg white should not contain cellular débris and do not cause coagulation when introduced intravenously, the two conditions under which Besredka advocated the use of the intrathecal route.

---

[8] Besredka: Ann. de l'Inst. Pasteur **21**:117, 1907.

[9] Gay, F. P., and Southard, E. E.: J. M. Research **21**:21, 1909.

[10] Pfeiffer: Die Arbeitsmethoden bei Versuchen über Anaphylaxie; Abderhalden, Handbuch der Biologischen Arbeitsmethoden, Pt. 13, 2, 1.

It seemed to me that if egg protein is demonstrable in breast milk when injected intrathecally, it should also be demonstrable by the intravenous route or by the Dale uterine strip method. Furthermore, owing to the foregoing considerations, I believe that the presence of this protein cannot be assumed to have been proved unless confirmed by one of these other methods. Wells[12] gives as one of the cardinal requirements for proof regarding the presence of a foreign protein that it be demonstrable by the uterine strip method. Shannon objects to the intravenous route because of the danger of embolism, but our cases, in many of which careful necropsies were performed and in none of which was evidence of embolism found, suggest that when skimmed milk or a filtered egg white dilution is used, this danger is not a real one. Furthermore, this argument could only apply to the interpretation of positive reactions, and could have no bearing upon the value of negative findings. As to the uterine strip method, Shannon mentions it, but does not say why he chose the intrathecal method in preference. The technic of the uterine strip test is far more time consuming, but the clean cut graphic results are well worth the additional labor. Certainly the tendency of the present day is to work only with the intravenous or the uterine strip methods when testing sensitized animals for the demonstration of antigen.

---

[11] Besredka, A.: Anaphylaxis and Anti-Anaphylaxis and Their Experimental Foundations, St. Louis, C. V. Mosby Company, 1919.

[12] Wells, H. G.: Physiol. Rev. **1**:44 (Jan.) 1921.

CONCLUSION

I believe that our experiments warrant the conclusion that egg white protein is not demonstrable in the breast milk of mothers by any of the methods at present at our command. I do not intend to suggest that such protein may not be present in infinitely small amounts, but knowing what small traces of egg white will sensitize guinea-pigs, I feel that the conclusion is warranted that infants must be extremely sensitive to be affected by the amounts which they receive from this source. The explanation, therefore, of the frequent finding of these positive reactions in exclusively breast fed infants has not as yet been given, and the problem calls for further investigation. My results, however, fail to suggest that breast milk is a medium for the transmission of antigen.

OXYGEN THERAPY IN PREMATURE BABIES WITH ANOXEMIA *

HARRY BAKWIN, M.D.
NEW YORK

By anoxemia is meant a condition in which the oxygen pressure in the systemic capillaries is abnormally diminished.[1] It is seen most frequently when the hemoglobin of the blood is less saturated with oxygen than normally. The difference between the amount of oxygen which the hemoglobin is capable of carrying (oxygen capacity) and the amount which it actually carries (oxygen content) is known as the oxygen unsaturation of the blood.

In normal adults Lundsgaard [2] found that the unsaturation of the venous blood varies from 2.7 to 9.0 c.c. of oxygen for each hundred cubic centimeters of blood, averaging 5.8 c.c. Our results with blood obtained from the longitudinal sinus of well infants (Table 1) are practically the same as those of Lundsgaard on blood from the median basilic vein of adults. The oxygen unsaturation varied from 5.1 to 8.3 c.c., averaging 6.7 c.c. Blood from a scalp vein is much more nearly saturated with oxygen than is longitudinal sinus blood. Arterial blood is normally about 95 per cent. saturated.[3]

METHODS

Oxygen capacity was calculated from the hemoglobin.[4] The oxygen content was determined by the Van Slyke and Stadie method.[5] The earlier estimations were made with the Van Slyke method.[6]

In cyanotic persons an increase in the oxygen unsaturation of the venous and arterial blood was demonstrated by Stadie [3] in pneumonia and by Harrop [7] in patients with uncompensated heart disease. Lunds-

---

* Received for publication, Nov. 21, 1922.

* From the Pediatric Service, New York Nursery and Child's Hospital and the Department of Pediatrics, Cornell University Medical College.

[1] Haldane, J. S.: Respiration, Yale University Press, 1922, p. 124.

[2] Lundsgaard, C.: Studies of Oxygen in the Venous Blood, I, J. Biol. Chem. **33**:133, 1918.

[3] Stadie, W. C.: The Oxygen of the Arterial and Venous Blood in Pneumonia and Its Relation to Cyanosis, J. Exper. M. **30**:215 (Sept.) 1919.

[4] Palmer, W. W.: The Colorimetric Determination of Hemoglobin, J. Biol. Chem. **33**:119, 1918.

[5] Van Slyke, D. D., and Stadie, W. C.: The Determination of Gases of the Blood, J. Biol. Chem. **49**:1 (Nov.) 1921.

[6] Van. Slyke, D. D.: The Gasometric Determination of the Oxygen and Hemoglobin of the Blood, J. Biol. Chem. **33**:127, 1918.

[7] Harrop, G. A.: The Oxygen and Carbon Dioxid Content of the Arterial and Venous Blood in Normal Individuals and in Patients with Anemia and Heart Disease, J. Exper. M. **30**:241 (Sept.) 1919.

gaard,[8] working with venous blood alone, obtained similar results. All three observers agree that cyanosis is closely related to an increase in the oxygen unsaturation of the blood.

Cyanosis is, therefore, distinct evidence of anoxemia. It occurs frequently in premature babies and may be associated with a number of different conditions, such as cerebral hemorrhage, pneumonia and sepsis. The cases of cyanosis with which this paper is concerned, however, are those which occur so frequently during the first few days of life in prematurely born babies and for which no assignable cause can be found, except a few atelectatic patches in the lungs. In these babies cyanotic attacks start soon after birth and recur more or less frequently for several days. If the baby lives through this period the attacks usually cease. Death, however, is an all too frequent sequel.

TABLE 1.—The Oxygen Unsaturation of Blood from the Longitudinal Sinus of Well Infants

Case	Oxygen Capacity-Volume per Cent.	Oxygen Content-Volume per Cent.	Oxygen Unsaturation	
			Volume per Cent.	Percentage
1	15.1	7.9	7.2	48
2	15.1	9.2	5.9	39
3	16.4	11.3	5.1	45
4	14.4	8.5	5.9	41
5	16.5	9.1	7.4	45
6	14.9	6.7	8.2	55
7	15.1	7.2	7.9	52
8	13.7	6.6	7.1	52
9	13.9	7.5	6.4	46
10	18.0	11.3	6.7	37
11	20.2	13.0	7.2	36
12	14.1	8.9	5.2	37
13	16.7	10.9	5.8	35

The cyanosis in premature babies is usually extreme and is accompanied, as in adults, by an increase in the oxygen unsaturation of the blood (Compare case histories). During the cyanotic attack the respirations become progressively slower and finally cease. The heart also beats slower and becomes weaker; but it usually continues to beat for several minutes after respiration has ceased.

THE MODE OF PRODUCTION OF ANOXEMIA IN PREMATURE BABIES

According to Holt[9] expansion of the lungs of the new-born is a gradual process requiring several days for its completion. In small, frail babies full expansion of the lungs may be delayed for several weeks. As a consequence, the blood flowing through the walls of the collapsed alveoli is poorly or not at all oxygenated, whereas in the expanded portion of the lungs the blood is normally arterialized. The mixed arterial blood coming from the lungs, therefore, is incompletely oxygenated, and anoxemia results.

---

[8] Lundsgaard, C.: Studies of Oxygen in Venous Blood, IV, J. Exper. M. **27**:219 (Sept.) 1918.

[9] Holt, L. E.: Diseases of Children, 1919, p. 69.

Evidence of the anoxemia in premature babies is found in the type of breathing so frequently seen in these babies. It is a matter of common clinical observation that the breathing in prematurely born infants is irregular both in rate and depth. Recently Eckstein and Rominger [10] obtained graphic records of the respiration. They found that it may be distinctly periodic in type and describe three varieties of periodicity. One type is that known as Cheyne-Stokes breathing, in which periods of hyperpnea are followed by periods of apnea. They have seen apneic periods lasting as long as ten seconds. In other cases, deep breaths alternate with shallow ones, the entire curve showing a wavelike rise and fall. The latter phenomenon they interpret as due to changes in the tone of the diaphragm. In a third type rapid, shallow respirations alternate with slow, deep ones.

According to Douglas and Haldane [11] periodic breathing is due to anoxemia. The stimulus of oxygen want, expressed physiologically by the decrease in the oxygen saturation of the blood, together with the carbon dioxid present, results in excitation of the respiratory center and hyperpnea. The hyperpnea relieves the oxygen want, and the breathing quiets down only to start up again when the oxygen deficiency reaches the stimulating point once more. Pembrey and Allen [12] have shown that Cheyne-Stokes breathing may be abolished by giving oxygen, thereby proving, Haldane believes, that this type of breathing is due to oxygen want.

EXPERIMENTAL STUDIES

The effect of oxygen on anoxemia in prematurely born babies was studied by comparing the saturation of the blood and the clinical condition before and after the administration of oxygen. The two babies selected for this study showed marked evidence of anoxemia. A large group of cases has been observed clinically during the past three years, but it did not seem advisable to make blood determinations.

Methods of Administering Oxygen to Babies.—In order that oxygen therapy may be of value, the oxygen must be properly given. The funnel method, which has been so widely used, is practically useless. Meltzer [13] estimated that by this method the inspired air is enriched by not more than 2 per cent. of oxygen. Haldane[14] devised an apparatus by which oxygen could be accurately and economically added to the inspired air. Oxygen was also given during the recent war with some success through a nasal catheter.[15] Excellent results have been obtained by various workers[16] with the oxygen chamber. Barach and Woodwell[17] found a rubber mouthpiece an effective means of giving oxygen.

---

[10] Eckstein, A., and Rominger, E.: Beiträge zur Physiologie und Pathologie der Atmung, Ztschr. f. Kinderh. **28**:1, 1921.

[11] Douglas, C. G., and Haldane, J. S.: The Causes of Periodic or Cheyne-Stokes Breathing, J. Physiol. **38**:401 (June) 1909.

[12] Pembrey, M. S., and Allen, R. W.: Observations Upon Cheyne-Stokes Respiration, J. Physiol. **32**:XVIII, 1905, (Proc. Physiol. Soc.)

[13] Meltzer, S. J.: The Therapeutic Value of Oral Rhythmic Insufflation of Oxygen, J. A. M. A. **69**:1150 (Oct. 6) 1917.

In prematurely born infants oxygen may be given effectively by means of two fine rubber catheters inserted into the nostrils. The catheters are well lubricated and connected to the oxygen tank by means of a Y tube. The oxygen may also be given through a rubber tube about 1 cm. in diameter, inserted into the mouth. The rubber tube is held in position by a glass collar which fits snugly over the tube. The collar is held in place with tape, which is tied back of the baby's head. Since the small babies move very little, the collar and tube are easily kept in place. Such a collar eliminates the need of a nurse in constant attendance during the oxygen administration. Occasionally when oxygen is given in this way, it is swallowed, and the abdomen becomes distended. In such cases, of course, the oral route should be abandoned.[18]

REPORT OF CASES

CASE 1.—*History.*—A baby boy, who was delivered normally and weighed 1,690 gm., began to have attacks of cyanosis shortly after birth, the attacks usually occurring soon after a feeding. The blood oxygen determinations were made one day after birth. At this time the baby was deeply cyanotic, the heart rate 20 per minute and the rhythm regular. The breathing was very shallow and irregular. The physical examination otherwise was negative.

Treatment.—Oxygen was given through a tube inserted into the mouth. After a few minutes the baby became bright pink, the respirations became deeper and the heart sounds stronger. The baby continued to have attacks of cyanosis for the next few days, particularly after his feedings. He was treated each time with oxygen, to which he reacted promptly. He was discharged from the hospital cured, and when last seen was 6 months old and apparently well, except for slight malnutrition.

Comment.—In this case the oxygen unsaturation which was very high before the oxygen administration (14.8 c.c. for each hundred cubic

---

14. Haldane, J. S.: The Therapeutic Administration of Oxygen, Brit. M. J. **1**:181 (Feb. 10) 1917.

15. Stokes, quoted by Cummins: Proc. Roy. Med. Soc. **13**:59, 1920.

16. Barcroft, J.; Hunt, G. H., and Dufton, D.: The Treatment of Chronic Cases of Gas Poisoning by Continuous Oxygen Administration in Chambers, Quart. J. M. **13**:179, 1920. Shufflebotham, F., and Sowry, G. H.: Proc. Roy. Med. Soc. **13**:59, 1920. Stadie, W. C.: The Treatment of Anoxemia in Pneumonia in an Oxygen Chamber, J. Exper. M. **35**:337 (March) 1922.

17. Barach, A. L., and Woodwell, M. N.: Studies in Oxygen Therapy with Determination of Blood Gases, Arch. Int. Med. **28**:367 (Oct.) 1921.

18. These methods may also be used in older infants. Often, however, the babies struggle against the tubes. In these cases the oxygen may be given in a tent constructed from sheets.

centimeters) fell to normal (5.5 c.c.) after the oxygen was given. The results of the blood examinations are shown in Table 2.

Case 2.—*History.*—A boy, the first child, was delivered normally and weighed 2,030 gm. Except for his small size he seemed normal. On the second day after birth it was noticed that he had attacks of cyanosis; at times he almost ceased to breathe. He was restored each time with counter irritation (mustard baths) and artificial respiration. The attacks became more and more frequent, and it was becoming increasingly difficult to revive him.

Examination.—The baby was seen during an attack on the third day. He was extremely cyanotic, spontaneous respiration having ceased. The heart rate was 15 per minute, and the sounds only faintly audible. There was sclero-edema of the skin over the abdomen and thighs.

Treatment.—Artificial respiration was used, but the apnea and cyanosis persisted. Oxygen was then given through a rubber tube in the mouth, and the artificial respiration continued. Within a few minutes the baby began to breathe spontaneously, the respirations becoming markedly periodic in type. As the oxygen was continued the baby became rosy pink in color, the respirations became more regular and the heart sounds improved in quality, the rate rising to 60. The oxygen unsaturation of blood from the longitudinal sinus fell from 13.1 to 7.7 c.c., which is within normal limits (Table 1). The results of the blood determinations are shown in Table 3.

The baby had several other attacks of cyanosis during the day and was revived each time with oxygen. The sclero-edema extended to the face and arms, and the baby died during the night. Necropsy was not permitted. There was no evidence of organic disease at any time, aside from the sclero-edema.

TABLE 2.—Increase in Blood Oxygen of Case 1 After the Administration of Oxygen

	Oxygen Capacity, Volume per Cent.	Oxygen Content, Volume per Cent.	Oxygen Unsaturation, Volume per Cent.	Color
Before oxygen	27.9	13.1	14.8	Extreme cyanosis
After oxygen	27.9	22.4	5.5	Rosy pink

TABLE 3.—Increase in Blood Oxygen of Case 2 After the Administration of Oxygen

	Oxygen Capacity, Volume per Cent.	Oxygen Content, Volume per Cent.	Oxygen Unsaturation, Volume per Cent.	Color
Before oxygen	15.3	2.2	13.1	Deep cyanosis
After oxygen	15.3	7.6	7.7	Rosy pink

COMMENT

In the two cyanotic infants studied the oxygen unsaturation of the venous blood before treatment was markedly increased, indicating a severe degree of anoxemia. The administration of oxygen resulted, in both instances, in a prompt return of the oxygen saturation to normal. The cyanosis disappeared, abnormal respiration was abolished and the heart rate rose to normal. One of the two babies treated was 6 months old when last seen and was apparently well, except for slight malnutrition. The other baby, who had sclero-edema at the time of treatment, died some time after the oxygen inhalations were discontinued.

During the past three years a large number of cyanotic premature infants have been treated with oxygen inhalations. The response to the oxygen is usually prompt, and but a few minutes are necessary before the cyanosis disappears and the character of the respirations changes. It is difficult to gage with any degree of accuracy the permanent value of oxygen to the babies. It did seem that, in general, when oxygen was administered early, the subsequent cyanotic attacks were fewer in number and more readily amenable to treatment.

With the methods employed (nasal catheters, mouth-tube), the oxygen could necessarily be given only over comparatively short periods of time. Though it was usually effective in remedying the immediate attacks of cyanosis, as a rule, the attacks recurred. In order that the full benefit of oxygen therapy may be obtained, it should be given over a long period of time. For this purpose the oxygen chamber is almost ideal.

SUMMARY AND CONCLUSIONS

1. The oxygen unsaturation of blood from the longitudinal sinus of well infants varies from 5.1 to 8.3 c.c., averaging 6.7 c.c.

2. The oxygen unsaturation of longitudinal sinus blood in two prematurely born babies with marked cyanosis was 14.8 and 13.1 c.c., respectively.

3. These two prematurely born babies with marked anoxemia, as indicated by the cyanosis and the increase in the oxygen unsaturation of the venous blood, were treated with oxygen inhalations. In both instances the cyanosis disappeared and the saturation of the venous blood rose to normal.

4. Oxygen may be given effectively to prematurely born babies through nasal catheters or through a rubber tube inserted into the mouth.

TOXEMIA OF SEVERE SUPERFICIAL BURNS IN CHILDREN *

BRUCE ROBERTSON, B.A., M.B. (Tor.)
AND
GLADYS BOYD, M.B.
TORONTO, CANADA

The very high mortality in cases of severe superficial burns and scalds in children has always occasioned grave concern. Against the mortality due to primary shock (which is comparable to primary traumatic shock) our resources are limited, and the nature of the injury is such that a much lower death rate from this cause is hardly to be expected.

An even higher mortality is encountered from toxic shock, and this condition we believe is more amenable to treatment than primary shock. However, under ordinary methods of treatment, there has been little reduction in the mortality due to toxemia, chiefly because attention has been directed more to the problems of local treatment than to relief of the early toxemia which frequently results in death. Despite advances made in improving local applications for burned surfaces, the death rate is still distressingly high. We can only come to the conclusion that within certain limits the type of local dressing has little effect on the immediate issue. The treatment of toxemia or toxic shock merits our most thoughtful consideration, since in the earlier stages of the burn it is the most important factor influencing the success of the final result.

Analysis of 100 Consecutive Cases of Severe Burns and Scalds Admitted to the Wards of the Hospital for Sick Children. None of These Were Treated by Transfusion or Exsanguination Transfusion

		0-2 Yrs.	2-4 Yrs.	4-8 Yrs.	8-12 Yrs.
Recovered		16	31	11	7
Died *	Primary shock	5	3	4	1
	Toxic shock	8	8	2	1
Total		29	42	17	9

* Three other children between 2 and 4 years died of bronchopneumonia, infection of burned area, and intestinal hemorrhage, respectively.

PROBLEMS ENCOUNTERED

The problems encountered early in cases of severe superficial burns in children are those of (*a*) primary shock and (*b*) toxemia or toxic shock.

---

* Received for publication, Dec. 15, 1922.

* From the Wards and Laboratories of the Hospital for Sick Children.

(*a*) *Primary Shock.*—When the primary shock is so intense that death may occur a few hours after injury, treatment directed toward relief of the shock is very disappointing, and the burn is usually so severe and extensive that it precludes the possibility of recovery either in the immediate or the remote future.

(*b*) *Toxemia or Toxic Shock.*—In a considerable number of cases the primary shock is mild or absent. Then follows an interval during which the general condition appears to be good—in fact, sometimes it is much better than the extent of the burn would warrant. But after the first twenty-four or forty-eight hours, the temperature begins to rise, and toxemia develops. The patient becomes drowsy, the pulse becomes more rapid and the circulation is somewhat depressed.

In cases going on to recovery the elevated temperature, and with it the toxemia, usually begins to subside about the fifth day, after which the problem becomes one of local treatment of the burn.

In the more severe cases, however, there is a greater rise in temperature, often to 106 F., and the toxemia is increased. Vomiting occurs as an early sign in fatal toxemia and becomes persistent. The pulse assumes a softer character, and the color tends to be dusky or livid, an evidence of capillary stasis. With the increasing toxemia, muscular twitchings occur, followed by convulsions. These usher in the final stage, and the patient dies after one or more convulsions.

The severity of the toxic symptoms corresponds to some extent with the area and depth of the burn. Second and third degree burns produce the most severe toxemia. There must, however, be individual differences, since we have seen comparatively small second and third degree burns produce fatal toxemia, while those of larger size have not been fatal. Age is an important factor: the younger the patient, the more severe are the symptoms with the same area involved. The situation of the burn also has some bearing on the severity of the symptoms. Those burns involving the chest and head usually produce more immediate and more severe symptoms than extremity burns.

Urinalysis.—In the great majority of burn cases the urine was found to be negative for albumin even in the stage of toxemia, although it was frequently reduced in amount at this time. In only a few cases was a trace of albumin found, and this was transitory.

Blood Findings.—In the early stages of the toxemia, the red blood cell count and hemoglobin were found to be slightly increased. This appears to be due only to concentration of the blood and is an evidence of the dehydrated condition of the tissues at this stage. The leukocyte count, however, may be increased, and we have seen it as high as 19,800 during the toxic stage. Increase in the leukocyte count several days after the burn is sustained is usually due to infection of the burned area.

In seven cases of burns, the nonprotein nitrogen content of the blood was estimated (G. B.) and was found to range from 42.9 to 99.0. The clinical application of these readings is not quite clear since in one case of recovery it reached 70.0, while in a fatal case it was 42.0. Again, in a case in which recovery followed treatment by exsanguination-transfusion, the reading was 42.9 at the height of the toxic stage, 46.21 five days later when the child had passed the critical stage, and 24.8, three weeks later, during convalescence.

It is probable that the increase of the nonprotein nitrogen is due to increased tissue destruction rather than to defective kidney elimination and is comparable to the findings of Rabinowitch[1] in intestinal obstruction. Our observations of the nonprotein nitrogen content in respect to burns are too few to warrant any conclusion as to prognostic importance.

From a purely clinical point of view, there seems to be no doubt that the burned tissues are responsible for the production of some toxin which is taken up by the blood stream. The appearance of toxic symptoms after the first twenty-four hours probably indicates that the damaged tissue must be in contact with living tissue before a toxic substance can be manufactured.

The nature of this toxin is not definitely known, but from the clinical symptoms, it would appear to be allied to the toxins produced in secondary wound shock and in intussusception. It differs from these toxins, however, in that it causes convulsions.

The treatment of these very severe cases of toxic shock in superficial burns in children offers a very definite problem. Every one admits, only to deplore, his helplessness when confronted with the case of a severely burned child in convulsions. In many of the cases the area of the burn would not constitute a surgical problem, but the toxic shock is likely to prove fatal.

RELIEF OF TOXEMIA

In casting about for some means of relieving the toxemia, two methods of attacking the problem were considered: (*a*) local treatment of the burn; (*b*) treatment of the toxemia, once it is established.

(*a*) The possibility of removing the damaged tissue either by excision or scrubbing was considered but was found to be impracticable, since in most of the cases the area was too large, or it involved regions such as the face, or the patients were admitted in the toxic stage.

The only chemical application which seemed to possess any value in diminishing the toxemia or retarding its onset was sodium bicarbonate in saturated solution. In conjunction with the local application, the drug was given by mouth to the limit of tolerance. By this means the bicarbonate content of the blood was found to be increased. Though its administration serves to decrease the so-called acidosis which is present and in this respect is only symptomatic treatment, its effect seemed to be favorable.

---

[1] Rabinowitch, I. M.: Canad. M. A. J. **11**:163 (March) 1921.

(*b*) It seemed to us that the simplest and quickest way of overcoming the toxin in the blood was to remove it. We assumed that removal of a sufficient quantity of blood might give the patient a chance to overcome further accessions of toxin. The freshly injected adult blood, even if it did not affect the toxin directly, would at least supply fresh nourishment to the tissues and help to reestablish a normal balance in the blood.

The assumption was not altogether theoretical, since we had had two burned patients who had convulsions and had recovered following straight blood transfusion.

To put into effect this idea, the operation of "exsanguination-transfusion" was devised in this hospital. The object was to withdraw a very much greater quantity of the patient's blood than could be obtained by simple venesection and to replace this with fresh adult blood. Briefly stated, the operation consists in the initial withdrawal of blood from the patient's longitudinal sinus or femoral vein until the limit of safety is reached. The transfusion is then commenced in an elbow vein. Withdrawal of the patient's blood and injection of fresh blood are then carried on simultaneously until the amount withdrawn is slightly less than the amount available for transfusion. The withdrawal is then discontinued and the remainder of available blood injected. The amount of blood withdrawn has ranged from 200 c.c. in an infant, up to 500 c.c. in a child of 3 years of age. It is obvious after the transfusion begins that a small but increasing percentage of the transfused blood is withdrawn. Notwithstanding this, the procedure in several cases appears to have turned the scales in favor of the patient. The technic is described in detail in a previous article.[2]

RESULTS

The results so far have been very encouraging. In ten cases of burns of the type described (i. e., with convulsions), two children received blood transfusion and eight were subjected to exsanguination-transfusion. Three of the latter died from burn toxemia. In the other seven cases, the burn toxemia was relieved.[3]

Under any method of treatment other than transfusion or exsanguination-transfusion, we have seen no burned patient recover after a convulsion has been precipitated as a result of the burn toxemia. In our opinion the operation of exsanguination-transfusion offers the better chance of recovery.

---

[2] Robertson, B.: Canad. M. A. J. **11**:744 (Oct.) 1921.

[3] One of these children died about two months later from a diphtheritic wound infection two weeks after operation for skin grafting on a different area.

Coincident with the progress of the clinical work, experimental work was being carried out. Full details of these experiments will be published later, but as the results furnish some substantiation for the theory on which the treatment described above is based, a brief summary of our results and conclusions might be of interest.

Our experiments show that there is a substance produced in burned tissues (in larger quantities in extensive skin burns than in those of other tissues) which circulates in the blood, either in, or closely adsorbed to, the red blood cells and which causes the symptoms of toxic shock, and in some cases death. The toxic material is produced in increasing amounts following the burning of the tissue until from twenty-four to thirty-six hours after the injury. It is produced only as a result of burning living tissues. The toxin is most highly concentrated in solutions of corpuscles suitably treated and least in the blood serum.[4]

Chemically, this toxin consists of primary and secondary proteoses. Like snake venom, it is made up of two portions, a necrotoxic and a neurotoxic. The former is not destroyed by heat and is diffusible; the latter is thermolabile and colloidal.

We were unable to obtain any evidence of the production of antibodies against this poison. Katzeroff[5] recently reported the finding of such antibodies. His evidence is based on the beneficial effects of convalescent serum from burned patients in fourteen cases of toxic shock and not on biologic tests.

---

[4] We have purposely not included in this paper the problems of secondary pyogenic infection of the burned area or the peculiar rash and temperature curve almost indistinguishable from scarlet fever which so frequently complicate the burn cases.

[5] Katzeroff, A.: Rev. de chir., 1922, p. 60; abstr. J. A. M. A. **79**:507 (Aug. 5) 1922.

PROGRESS IN PEDIATRICS

A REVIEW OF THE LITERATURE ON THE BLOOD AND BLOOD DISEASES OF INFANTS AND CHILDREN FOR THE LAST FOUR YEARS (1918-1921) *

LEWIS WEBB HILL, M.D.
BOSTON

Although innumerable papers on the blood have appeared in the last few years, the proportion of really valuable contributions is small, and a great deal of the literature is unimportant from the reviewer's standpoint. The outstanding advances are an increase in knowledge of the blood chemistry in children, especially in the new-born, and in marasmic and intoxicated infants, and valuable contributions to our understanding of hemorrhagic disease of the new-born, aplastic anemia and alimentary anemia. There have also appeared important articles dealing with the classification of the "hemorrhagic diseases," and many contributions concerned with improved technic for transfusion.

THE BLOOD IN NEW-BORN INFANTS

Lucas,[1] Dearing, Hobler, Cox, Jones and Smith, in an extensive investigation of the blood of normal new-born infants, report the following: The blood in a large series of infants was studied from a few hours after birth up to the fourteenth day. The hemoglobin and red blood cells were found to show high values during the first few days, with a decided drop during the second week. Nucleated red cells were present in 52 per cent. of all cases on the first day, and in only 5 per cent. on the second day. There was also found to be a considerable variation in the size of the red cells for the first few days. The white blood cells varied from 19,200 on the first day to 13,200 on the twelfth day. The leukocytosis is due to increase in the number of polymorphonuclears during the first week; after which the lymphocytes begin gradually to increase. The average platelet count was from 305,000 on the first day to 266,000 on the eighth day. The platelets were not reduced in cases in which the coagulation was prolonged.

Blood Chemistry.—The urea and nonprotein nitrogen were about the same as in adults. The values for calcium were somewhat higher in the new-born than in older children, an average of 12.3 mg. for each hundred cubic centimeters of blood. (The normal value for older infants is from 10.8 to 11.5 mg. for each hundred cubic centimeters.)

---

* Received for publication, Dec. 15, 1922.

[1] Lucas, W. P., et al.: Blood Studies in the New-Born, Am. J. Dis. Child. **22**:525 (Dec.) 1921.

"These calcium determinations show that in the blood of the new-born infant, calcium is rarely at fault in any problem related to hemorrhage, except in those cases of obstructive jaundice in which the calcium is bound by the bile salts and is, therefore, unavailable for entering into the process of coaggulation."

Coagulation.—In the first four days there is a definite prolongation in the coagulation time, whether hemorrhage occurs or not. This was prolonged in some cases to as long as thirty or forty minutes without the appearance of hemorrhage or increase in bleeding time. The average bleeding time is from one and one-half to three minutes.

Bile.—In seventy-two of ninety cases bilirubin was found in the plasma. Sedgwick[2] found that in the new-born the values for creatin plus creatinin and nonprotein nitrogen are high, corresponding to the high values for uric acid during that period. The creatinin and sugar values are essentially the same as the adult normal values, and the urea nitrogen is near the maximum normal value for adults.

Happ,[3] in 1919, studied the iso-agglutination reaction of 131 infants and children from birth to ten years. He found that at birth, and during the first month, iso-agglutination is rarely present, but the percentage of infants in whom the iso-agglutination group is established increases with age, so that after one year the group is usually established, and after two years it is always present as in adults.

Iso-agglutinins were found to be present in human milk, and the grouping was identical with that of the mother's blood.

Jones[4] studied the iso-agglutinins in the blood of new-born infants, and found that 78.7 per cent. of 197 specimens of blood could be placed definitely in one of the four recognized iso-agglutination groups. This percentage is much higher than any previously reported, and these results are probably dependent on a technic which permits the recognition of weak agglutinins.

Rodda,[5] in an important investigation on the coagulation time of the blood of new-born infants, describes a simple, practical method for determining this with small amounts of blood. This is of considerable value, as there was previously no very satisfactory method for use in small babies. The apparatus necessary consists of a spring lance, two 1½ inch watch glasses, and a No. 6 lead shot. The glasses and shot are cleaned with soap and water, followed by alcohol and ether. The heel of the infant is sponged with ether, a puncture is made with the lance blade, set at 0.5 cm. to produce a free flow of blood without the slightest pressure. A watch glass containing the shot receives the second drop of blood; a second watch glass is inverted over the first, and the watch glasses are gently tilted every thirty seconds until the shot no longer rolls, but is fixed in the clot. The end point is sharply defined, the shot is firmly embedded, so that the glass may be inverted without dislodging it. The greatest source of error is concerned with the blood flow. A small, slowly forming drop obtained by pressure clots very quickly. The blood flow must be free and must occur without pressure or squeezing. The first drop is discarded, the second drop only is used, and the time is reckoned from the moment when the first drop fell. No claim is made that the method is absolutely accurate, but the object is to find gross variations from a normal range.

---

[2] Sedgwick, J. P., and Ziegler, M. R.: Nitrogenous and Sugar Content, Am. J. Dis. Child. **19**:429 (June) 1920.

[3] Happ, W. M.: J. Exper. Med. **31**:313 (March) 1920.

[4] Jones, B. B.: Iso-Agglutinins in the Blood of the New-Born, Am. J. Dis. Child. **22**:586 (Dec.) 1921.

[5] Rodda, F. C.: Determining Coagulation Time of Blood in the New-Born, Am. J. Dis. Child. **19**:268 (April) 1920.

By this method on 126 new-born infants within the first twenty-four hours of life, the average coagulation time was found to be seven minutes. A range of from four to ten minutes included 95 per cent. of the cases. Thus it may be said that with this method more than ten minutes means delayed coagulation. A bleeding time of from two to five minutes may be considered normal for the new-born infant. In the normal new-born infant there is found a tendency to prolongation of these times in the first few days.[6]

Schloss,[7] in a careful study of the blood in "intestinal intoxication" in infants, found that the nonprotein nitrogen was greatly increased, from 57 to 232 mg. per hundred cubic centimeters of blood. In normal infants it was found to be from 23 to 39 mg. per hundred cubic centimeters of blood. He found that there was no constant decrease of the blood plasma in relation to corpuscles, which proved that the high nonprotein nitrogen cannot be explained on the basis of increased blood concentration. He showed by a very painstaking series of experiments that there is, in these cases, a considerably decreased renal function, largely caused by dessication, and that the increased nonprotein nitrogen of the blood is largely due to this. He believes that "intestinal intoxication" and uremia are comparable conditions.

Utheim [8] studied the water content of the blood in various conditions in infancy. As a rule, the younger organism contains more water than the mature organism. Prematurely born infants have a high water content of the blood, and do not acquire the water content of a normal

---

6. Rodda, F. C.: The Coagulation Time of Blood in the New-Born, J. A. M. A. **75**:452 (Aug. 14) 1920.

7. Schloss, O. M.: Intestinal Intoxication in Infants, Am. J. Dis. Child. **15**:165 (March) 1918.

8. Utheim, K.: Study of Blood and Its Circulation in Normal Infants and in Infants Suffering from Chronic Nutritional Disturbance, Am. J. Dis. Child. **20**:366 (Nov.) 1920.

infant's blood until they are about 3 months of age. In athrepsia the water content is high and the protein content of the serum low. The high water content of the blood in athrepsia and prematurity might be considered one of the factors which explain their low immunity

The serum protein in normal infants ranges from 6 to 6.5 per cent. and remains at this level until the tenth or eleventh month, when it begins to rise, until, by the fifteenth month, it has reached the same level as in adults (about 8.7 per cent.). Infants with acute diarrhea and vomiting show a high percentage of serum protein, the result of blood concentration. Prematurely born infants and athreptics show a low serum protein, often as low as 4 per cent. There is also a low rate of blood flow, due sometimes to diminished blood volume, and sometimes to constriction of the small peripheral vessels. Marriott and Sisson [9] found that the average blood fat in infants was 0.68 per cent., somewhat higher than the figure of 0.59 per cent. for normal adults (Bloor). They found that (1) the blood fat is independent of the nutritional state of the infant. (2) Infants who are gaining show usually a distinctly higher blood fat than those whose weight is stationary or dropping. (3) Breast fed infants who are gaining weight have a high blood fat.

Greenthal [10] studied the fragility of the red blood cells to hypotonic salt solution. He found that (1) there is no distinctive reaction to the fragility test in the infectious diseases. (2) Fever per se has no effect on the fragility of the red cells. (3) In certain cases of infectious disease one may find a distinct increase of resistance. These cases are usually of great severity, and the prognosis is grave. It is conceivable that a compensatory mechanism causes the red blood cells to protect themselves against an injurious toxin by an increase in their resistance to hemolytic agents.

HEMORRHAGIC DISEASE OF THE NEW-BORN

Warwick [11] reports thirty-six routine necropsies performed on stillborn babies, or those dying soon after birth. In this series eighteen showed definite hemorrhages in the dura, over the brain, or in the ventricles. In eight of these cases, gross hemorrhages were found in other organs besides the brain. Is thus appears quite clear that in a fairly large percentage of cases showing intracranial hemorrhage such lesions are merely incidental to a general hemorrhagic diathesis.

Early recognition of decreased coagulability of the blood, and prompt treatment by injections of whole blood are to be desired.

---

[9] Marriott and Sisson: Tr. Am. Pediat. Soc. **30,** 1920.

[10] Greenthal, R. M., and O'Donnell, W. S.: Fragility of Red Blood Corpuscles in Infectious Diseases, Am. J. Dis. Child. **22**:212 (Aug.) 1921.

[11] Warwick, M.: Am. J. M. Sc. **158**:95 (July) 1919.

ANEMIA AND THE "HEMORRHAGIC DISEASES"

Weill and Dufourt [12] describe "alimentary anemia" in infancy. The blood picture is characterized especially by a considerable deficiency of hemoglobin with but comparatively little drop in the red cell count. They believe that it is especially likely to occur in babies who start life with an insufficient supply of iron in the liver (prematurely born; twins) and in babies whose mothers had some wasting disease during pregnancy, such as tuberculosis, anemia or diabetes. It is probable that this type of anemia does not develop readily except in babies previously prepared for it by a poor condition of the mother. They quote Schmidt, who was unable to produce an anemia in experimental animals by feeding an iron poor diet, but the animals of the second generation were markedly anemic.

Schwarz and Rosenthal [13] describe what they call a "chlorotic type of anemia" in young infants, for which iron is a specific. Their cases correspond closely to those described by Weill and Dufourt. The disease may begin in early infancy but may not be apparent until the baby is 12 or 15 months old. It occurs especially in prematurely born infants and in twins. The hemoglobin is markedly diminished, but the red cell count rarely falls below 3,000,000. The color index is usually between 0.4 and 0.6. The anemia is usually cured by iron, which should be given in the form of iron containing foods as well as in the form of drugs.

Schwenke [14] discusses "severe anemia in early infancy." She recognizes two broad groups. The first group is characterized by a retardation of bodily and mental development, and shows a blood picture of pseudochlorosis; the second group shows, as the most striking sign, an enlarged spleen and a reversion of the blood morphology to an embryonic type. There were nine infants in the first group. All had been delicate and pale since birth. All but one were bottle fed, and had been overfed with milk, with but little solid food after the nursing period. They ranged in age from 1 to 3 years when first seen. Signs of rickets were insignificant or lacking, and the liver and spleen were not enlarged. The blood picture was characterized especially by a low hemoglobin percentage. In six cases it was from 15 to 25 per cent.; in three cases from 30 to 45 per cent. The red blood count was less diminished, and the white blood count and differential count were normal. The blood smear showed especially achromia, no polychromatophilia, and only very slight differences in size and shape of the

---

12. Weill, E., and Dufourt, A.: Anemia in Infants, Arch. de méd. d. enf. **24**:265 (May) 1921.

13. Schwarz, H., and Rosenthal, N.: Arch. Pediat. **37**:1 (Jan.) 1920.

14. Schwenke: Jahrb. f. Kinderh. **88**:181, 1918.

red cells, with but very few normoblasts. The platelets were present in normal numbers. In most of these cases there had been a good deal of difficulty in giving solid food when it was first started.

In most of Schwenke's cases there was congenital debility, either prematurity, or the babies were very small and feeble. All of the babies had been fed on practically nothing but milk. Rickets plays but little, if any, part in the etiology.

TREATMENT

Milk was considerably reduced in quantity (down to 10 ounces a day), and vegetables, fruit and meat were added to the diet. It usually took from three to six months to effect a cure. It was found that by greatly reducing milk, and adding vegetables and meat, a great deal of improvement resulted up to a certain point; then a standstill was likely to occur, which could not be influenced by iron, arsenic, or anything else. Schwenke believes that a one-sided milk diet is only part of the cause of the condition, and that congenital debility is far more important. It is a congenital dysfunction of the red blood forming organs. If other external agencies, such as infections, attack the child, the simple chlorotic type may take the form of a severe aplastic anemia, and the child may die. Only one necropsy was held in the series, and this showed a bone marrow relatively poor in cells, especially in myelocytes and nucleated reds.

Franzig[15] believes that the idea of Czerny's, which has also been advanced by Finkelstein, that the milk or milk fat has an active part in producing the alimentary type of anemia, has but little evidence to support it. He reports six cases of this type of anemia, the infants having been fed too long on a one-sided milk diet.

The children he treated received plenty of milk, well over 1½ ounces per pound of body weight, and a liberal caloric intake, furnished by the addition of sugar and starch. He added no vegetables as such, or meat, to the diet, but used a specially prepared extract of carrots, containing a great deal of iron. In most cases, after from four to ten weeks, there was a hemoglobin increase of from 20 to 30 per cent. He believes that the vegetable extract is much superior to vegetables without such preparation, as there is much less danger of producing digestive upsets.

Brinchmann[16] was able to produce an anemia of the chlorotic type in guinea-pigs by means of an iron poor diet. He found that by adding iron to the diet in medicinal form he was able to prevent the anemia, which is a rather significant fact, as it would indicate that in the alimentary type of anemia in infancy inorganic iron may be a valuable prophylactic and therapeutic agent, a point which is in some dispute. He found that there was no difference in the anemia of prematurely born infants, whether they were naturally or artificially fed.

---

[15] Franzig: Deutsch. med. Wchnschr. **47** (April 14) 1921.

[16] Brinchmann, A.: Ztschr. f. Kinderh. **30**:158 (Sept. 5) 1921.

Lichtenstein[17] has made an interesting and important study of the iron metabolism in premature infants in an attempt to explain the anemia which they so frequently develop. According to him, the only investigation of iron metabolism in infancy in the literature which can be accepted as free from errors is that made by Langstein and Edelstein in 1914, who found that breast fed babies retained from 0.12 to 0.25 mg. of iron per day, on an intake of from 0.55 to 0.65 mg.

Lichtenstein studied thirty-six healthy, prematurely born infants at about the third month of extra-uterine life, and found an average hemoglobin of 40 per cent., with about three million red cells per cubic millimeter.

Careful metabolism experiments made on four prematurely born babies showed that there was a negative iron balance in each of about 0.25 mg. daily. These babies were all fed on human milk, and were doing well. He has shown definitely that in prematurely born babies the amount of iron excreted is greater than the amount taken in with the food; this loss, after a while, causes a chlorotic type of anemia of fairly severe degree. The negative iron balance is explained by the fact that in prematurely born babies there is not a sufficient reserve supply of iron in the liver, as this reserve is largely deposited in the last two months of pregnancy. Lichtenstein gave one of these babies 50 mg. of iron per day in the form of ferric chlorid, and found that instead of the previous negative iron balance there was a positive balance of 1.7 mg. per day, and he says that in giving iron as a drug it is undoubtedly true that only a very small portion of the iron given is absorbed, but inasmuch as the iron needs are so minute, this is likely to be enough.

Whipple, Hooper and Robscheit[18] extensively investigated the regeneration of red cells and hemoglobin following simple anemia in dogs, produced by hemorrhage and the influence of dietary factors on this regeneration. They bled dogs one-fourth of the determined blood volume on each of two successive days. They found that under carefully controlled experimental conditions a diet of mixed table scraps will effect complete blood regeneration (to normal) in from four to seven weeks. Under similar experimental conditions there will be little blood regeneration during a fasting period. During sugar diet periods the regeneration of hemoglobin and red cells is distinctly less than during fasting periods. They explain this by the fact that during fasting a certain amount of body protein is broken down to supply the metabolic needs of the body, and that part of this is probably used in blood regeneration, but that during sugar feeding the carbohydrate intake acts as a nitrogen sparer, and not so much body protein is made available for purposes of blood regeneration.

---

[17] Lichtenstein: Acta Pediat. **1**:2, 1921.

[18] Whipple, G. H., Hooper, C. W., and Robscheit, I. S.: Am. J. Physiol. **53**:151 (Sept.) 1920.

A diet of dried white bread and skimmed milk may cause a slow steady gain in blood pigment volume from week to week, and a liberal diet of this type, sufficient to maintain body weight, will often suffice for complete blood regeneration. Rice, potatoes and skimmed milk may be classed with bread and milk. Cooked liver and meat are most efficient, when added to the standard diet, in causing increased blood regeneration, and a diet of this type will bring back the blood to normal within three weeks.

Iron in the form of pills of ferrous carbonate (Blaud's pills) was found to be entirely without effect on blood regeneration, nor were ferric citrate or ovoferrin found to exert any appreciable influence.

TABLE 1.—Blood Diagnosis (Ottenberg)

	Coagulation	Bleeding Time	Platelets
Hemophilia	Greatly prolonged	Normal or plus	Normal
Hemorrhage of new-born	Greatly prolonged	Prolonged	
Purpura hemorrhagica	Normal	Greatly prolonged	Greatly decreased
Purpura, secondary to			
1. Jaundice	Prolonged		
2. Chloroform	Prolonged		
3. Scurvy	Normal	Normal	Normal
Purpura simplex	Normal	Normal	Normal
Arthritic purpura			
Visceral purpura			

Iron in the form of hemoglobin may be concerned in the somewhat favorable action observed after feeding this by mouth. But the chances are that the iron is less important than the pyrrol ring. Arsenic was also found to be inert. No drug has been tested which can compare with the factors in meat for stimulating a rapid regeneration of blood following hemorrhage.

"These carefully controlled experiments give no support to the time honored custom of administering iron and certain other drugs in simple anemia. The burden of proof rests with those who claim that any given drug is potent under such conditions. . . . Those who claim that iron is a potent drug must exclude the food factors which are known to be concerned before they can prefer any objection to these statements." [19]

---

[19] It must be remembered that this work was done with one sort of anemia —that due to massive hemorrhage—and that it does not necessarily apply, and indeed probably does not apply, to the "alimentary anemia" which has already been discussed, a totally different form of anemia, probably directly dependent on an iron deficiency.—L. W. H.

HEMOPHILIA, APLASTIC ANEMIA, PURPURA, LEUKEMIA, ETC.

Ottenberg[20] gives in clear tabular form some of the differences between the various "hemorrhagic diseases." He also describes the following simple method of counting the blood platelets: "The blood is diluted in the counter exactly as for making a red count. It is then placed in the counting chamber and let stand for at least ten minutes in order to allow the platelets to settle. They are then counted in the same manner as the red cells, except that on account of their relative scarcity about ten times as many squares ought to be counted."

Aplastic Anemia.—Smith[21] collected in the literature from 1888 to December, 1918, sixty-four cases of this rare disease. It is a most severe disease, characterized by its rapid and progressively fatal course. No patients have been known to recover. Hemorrhagic manifestations, such as nosebleed or purpura, are almost always associated with it. There is usually a tremendous degree of anemia, and very large drops in the red cell count may take place with extraordinary rapidity. The skin may or may not show pigmentation.

TABLE 2.—Archibald's Diagnostic Points Between Aplastic Anemia and Pernicious Anemia

	Aplastic Anemia	Pernicious Anemia
Onset	Usually early in life	In adult life
Etiology	Unknown	Unknown
Progress	Acute and rapid	Slow and chronic
Remissions	None	Remissions present
Hemorrhages and petechiae	Common	Not common
Fever	Usually present	Usually absent
Mouth	Not sore	Sore
Numbness	Absent	Present
Color index	Low	High
Leukopenia	Yes	Yes
Small lymphocytes	Relative increase	Relative increase
Regeneration	No evidence	Evidence
Blasts	Absent	Present
Hemolysis	No evidence	Evidence
Bone marrow	Aplastic	Hyperplastic

No definite etiology has yet been found. Archibald[22] believes that there are borderline cases between aplastic and pernicious anemia, and that some relation may exist between the two conditions. Some of the reported cases show an extreme aplastic condition of the bone-marrow, with little or no hemolysis, while others show hemolysis as well as a failure to regenerate blood cells.

The differences between aplastic and pernicious anemia are shown in Table 2.

---

20. Ottenberg, R.: M. Clinics N. America **2**:289 (July) 1918.
21. Smith, L. W.: Aplastic Anemia, Am. J. Dis. Child. **17**:174 (March) 1919.
22. Archibald, A.: M. Clinics N. America **3**:757 (Nov.) 1919.

Larrabee,[23] in an excellent discussion, says that the especial significance of aplastic anemia is a poor function on the part of the bone marrow, failing to produce a normal number of red blood cells.

The view has often been expressed that aplastic anemia is merely pernicious anemia without regenerative changes in the marrow. Larrabee does not agree with this, and thinks that there is more reason for believing that aplastic anemia may result from some of the factors usually causing ordinary secondary anemia. Hemorrhage or severe sepsis may result in exhaustion of the marrow. Poisons, such as benzene, may produce an anemia closely allied to aplastic anemia. In leukemia, also, one may find similar changes. These are all secondary forms of aplastic anemia, but there is a large group in which the function of the marrow is inhibited from unknown causes, and the patient becomes anemic from the ordinary process of blood destruction.

The most striking features of the disease are the anemia and the marked tendency to bleed. The platelets are much decreased. Whereas the normal count is about 300,000, they may be reduced to only a few thousand. Coagulation time is prolonged, and the clot, when it does form, does not retract. The bleeding time is also prolonged. Subcutaneous hemorrhages are present in almost every case. The blood picture is definite: the red cells and hemoglobin are greatly diminished, usually in about the same proportion. Abnormalities in size and shape are slight, and nucleated red cells are usually absent. The white cells are also decreased, and the deficiency is confined to the polymorphonuclear neutrophils, eosinophils and mast cells.

Besides aplastic anemia there are other conditions in which the marrow is partially deficient. Purpura hemorrhagica is the most important of these. This is probably a form of aplasia involving only the platelet producing function of the bone marrow. In purpura hemorrhagica there is no aplasia either of the red or white cell producing functions. In this disease the aplasia is therefore only partial, and, if platelets are supplied by a transfusion, the hemorrhages are usually stopped for a few days. It is probable that some patients will recover entirely.

Musser[24] believes that aplastic anemia is an anemia secondary to primary bone marrow changes, and is not the result of hemolysis. It is a type of anemia in which the blood changes are dependent entirely on changes in the marrow, which, in turn, probably becomes pathologic as a result of some toxin which has a predilection for it. It is quite different from the so-called pernicious type of anemia, in which the bone

---

23. Larrabee, R. C.: Aplastic Anemia and Related Conditions, J. A. M. A. **75**:1632 (Dec. 11) 1920.

24. Musser, J. H., Jr.: M. Clinics N. America **3**:1403 (March) 1920.

marrow is red and hyperplastic and is presumably putting out a large number of cells, which are rapidly destroyed.

Rosenfield[25] reports two cases of idiopathic purpura with extensive and repeated hemorrhages into the capsule of the joints, a rather rare condition.

Larrabee[26] discusses the treatment of the "hemorrhagic diseases" (purpura, hemophilia, etc.). Appropriate treatment will almost always stop the bleeding, but the control is only temporary: the tendency to bleed will sooner or later recur, except in the few cases in which the causative disease is itself temporary. Local applications of styptics, such as ferric chlorid and epinephrin, are not very satisfactory. Cephalic and other tissue extracts are of somewhat more value. Calcium salts are of value only when the hemorrhage is due to calcium deficiency (chronic obstructive jaundice).

Fresh animal serum contains prothrombin, the coagulating element which is deficient in hemophilia and in hemorrhagic disease of the new-born. It does not contain platelets, and so is valueless in hemorrhagic purpura and other diseases in which the bleeding is due to platelet deficiency. Old serum is absolutely valueless. Transfusion with whole blood is the best thing for almost all of these cases, as it supplies all the elements for coagulation. If facilities for transfusion are not at hand, intramuscular injections of the whole blood are valuable, especially in the tissues near the bleeding area.

Condat[27] reports a case of "pernicious" anemia in a girl, aged 12 years. The hemoglobin was 25 per cent.; the red blood count, 780,000; the white count, 6,560. No nucleated red cells were seen, and no mention is made of the platelets. The general size of the red blood cells was large, and there was slight anisocytosis, otherwise there was nothing remarkable. The patient died, and there was no necropsy.[28]

Ward[29] discusses the so-called von Jaksch type of anemia. He believes that in this disease we are dealing with a hyperplastic process in the lymphoid tissues similar to leukemia, but on a lower plane. In infants with rickets, which is almost universally present in this type of anemia, there is a peculiar liability for the response to chronic infections to assume the characteristics of a leukemia rather than to show the more usual polymorphonuclear leukocytosis. Von Jaksch anemia may be regarded as a secondary or symptomatic leukemia, and represents the reaction of the blood forming tissues of rachitic infants to an organism or organisms which can produce the disease in a favorable soil. It is one of those progressive morbid processes which are sometimes termed symptoms, sometimes diseases.

---

[25] Rosenfield: Boston M. & S. J. **183**:89 (Aug. 5) 1920.

[26] Larrabee, R. C.: Boston M. & S. J. **183**:151 (Aug. 5) 1920.

[27] Condat: Arch. de méd. d. enf. **24**:676 (Nov.) 1921.

[28] This cannot be accepted as an authentic case of pernicious anemia, as there is not enough evidence to rule out aplastic anemia. It was possibly a case of the latter disease.

[29] Ward, G.: Brit. J. Dis. Child. **15**:101 (April-June) 1918.

The combination of a large spleen and anemia does not justify the diagnosis except when it occurs in infancy and is associated with rickets and infections. The conditions present in rickets are in some way responsible for the reaction to infection taking the form it does. Infection is the exciting factor, rickets the predisposing factor.

Evans and Happ,[30] after an excellent study of secondary anemia in young children, with and without enlargement of the spleen, believe that the so-called "von Jaksch disease," or "anemia infantum pseudoleukaemica" is not a disease of itself, but represents merely a secondary anemia due in most cases to unknown causes. The enlargement of the spleen, which may or may not be present, represents a peculiarity of reaction of the infant's hematopoietic system to anemia, and is not of particular significance. Neither is the mononuclear leukocytosis, which is likely to be present, significant, and likewise represents a special reaction on the part of the infant to anemia. It certainly bears no relationship to leukemia.

"The symptom complex usually called 'von Jaksch disease' can best be interpreted as the peculiar type of reaction on the part of the infant to the presence of a factor producing anemia, and should not be regarded as a disease *sui generis*. Rickets is frequently associated with *it,* but the condition is probably not caused by rickets.

Amesse[31] reports a case of Banti's disease in a boy, aged 6 years, who was cured by splenectomy. He made a good operative recovery, and soon after the hemoglobin rose from 30 per cent. to 70 per cent. and the red count became normal.

Canelli,[32] who has had much experience with Banti's disease in children, says that hemorrhage is one of the earliest symptoms, that glandular swelling is often present and that splenectomy is most beneficial when undertaken early in the course of the disease.

Leukemia.—There is nothing essentially new in the etiology or treatment of lymphatic leukemia, the usual form of this disease in childhood. It is uniformly fatal, usually in a short period of time, although transfusions may prolong the course.

Martelli[33] believes that there is a condition of infection of some sort usually associated with leukemia and that the disease is probably brought about by chronic infection.

---

[30] Evans, F. A., and Happ, W. M.: Bull. Johns Hopkins Hosp. **33**:1 (Jan.) 1922.

[31] Amesse, J. W.: Colorado Med. **17**:12 (Jan.) 1920.

[32] Canelli, A. F.: Pediatria **29**:832 (Sept. 15) 1921.

[33] Martelli, C. D.: Pediatria **26**:15 (Jan.) 1918.

In forty-five cases of acute leukemia he found an associated tuberculosis, syphilis, malaria, or pyogenic infection.

Baastrup[34] reports three cases of acute leukemia in which at, or before, the onset there was severe mouth infection, with tonsillitis and stomatitis. He believes that the disease is of infectious origin, and that its course often closely resembles that of acute sepsis.

Smith[35] reports what is probably the youngest case of lymphatic leukemia on record. A baby, 3 weeks old, began to vomit and to show loss of weight. Physical examination revealed an enlarged axillary lymph node, as large as a walnut, which the mother said had been present since birth. The spleen was also considerably enlarged, and there were ten or twelve purpuric spots scattered over the body. The white blood count was 189,000, 97 per cent. of which were lymphocytes.

GAUCHER'S DISEASE

Foot and Ladd[36] report a case of this rare disease lacking many of the usual symptoms. There were enlarged spleen, pain in the abdomen and legs, and profuse sweating. Splenectomy was performed, with most gratifying immediate results. "We know that the disease is fatal if untreated, or if treated by any other means than radical operation; we likewise know that splenectomy will afford very marked temporary relief from symptoms and improvement in general health. With these facts in view early splenectomy is therefore the treatment to be for the present recommended."

TRANSFUSION

In the last four years 229 articles dealing with various aspects of transfusion have appeared. The technic has been considerably improved, and transfusion has become a much more widely used procedure than it was five years ago. This is due to simplification of technic, so that it may be done with rather simple apparatus, and comparatively slight surgical experience. There are three methods of transfusion in general use, the citrate method, the syringe-cannula method of Lindeman, and the paraffin tube method of Kimpton and Brown, which was one of the earliest simplified methods of transfusion to be described. From a study of the literature, it is apparent that at the present time the citrate method (adding sodium citrate to the blood in order to prevent clotting) is by far the most popular, and although it unquestionably has certain disadvantages, its ease of performance makes it much more practical for the average medical man, and much more widely applicable than either of the other methods.

---

[34] Baastrup: Ugesk. f. Læger **80**:5 (Jan. 3) 1918.

[35] Smith, L. W.: Acute Leukemia in an Infant, Am. J. Dis. Child. **21**:163 (Feb.) 1921.

[36] Foot, N. C., and Ladd, W. E.: Gaucher's Splenomegaly, Am. J. Dis. Child. **21**:426 (May) 1921.

Koplik[37] discusses the indications for transfusion. In the new-born they are as follows: (1) uncontrolled hemorrhage from wounds, umbilicus or scalp hematoma; (2) frank melena; (3) concealed melena in which the outward objective signs of hemorrhage are slight, but in which the evidence of internal hemorrhage is great; (4) cases of severe and continued hemorrhage in the new-born caused by surgical wounds, such as circumcision.

Koplik believes in immediate transfusion for hemorrhagic disease of the new-born, rather than subcutaneous injection of blood. He emphasizes cases in which the subcutaneous injection of blood has failed, and transfusion has had to be resorted to.

Kimpton[38] discusses his experience with transfusion in more than 200 cases. He is a strong advocate of the paraffin tube method, using uncitrated blood. He calls especial attention to the possibility of anaphylaxis, even after the bloods of the recipient and donor have been tested for agglutination and hemolysis, and reports one death due to this.

There is no condition in which transfusion, used at the right time, gives better results than it does in hemorrhagic disease of the new-born.

Kimpton believes that transfusion should be performed immediately in a baby having enough hemorrhage to show clinically because one never knows when further hemorrhage may suddenly occur, and prove fatal. From 60 to 100 c.c. of blood is enough. Kimpton has never seen an untoward reaction of any sort due to transfusion in the new-born, and does not believe that it is necessary to group the bloods preliminary to transfusion. He has used the father as a donor in nearly all cases, without previous blood grouping.

In hemophilia the mother is not necessarily contraindicated as a donor, provided agglutination tests are made. He does not believe in the citrate method of transfusion, largely on account of the much greater liability to untoward reaction, whereas with the paraffin tube method, using citrated blood, the occurrence of reaction is very rare. He describes the technic of this method in detail.

One of the disadvantages of most of the agglutination tests is that sample serums of Types II and III are necessary, which is a considerable disadvantage from the standpoint of the general practitioner.

Kimpton describes a very simple test for agglutination, which can easily be performed at the bedside.

Donor's Blood.—(1) From 2 to 3 drops of blood plus 0.5 per cent. oxalate (or salt) solution = corpuscles. (2) From 2 to 3 drops of blood plus distilled water = serum.

---

37. Koplik, Henry: Tr. Am. Pediat. Soc. **31**:96, 1919.
38. Kimpton, A. R.: Boston M. & S. J. **178**:351 (March 14) 1918.

Recipient's Blood.—(3) From 2 to 3 drops of blood plus 0.5 per cent. oxalate (or salt) solution = corpuscles; (4) from 2 to 3 drops of blood plus distilled water = serum. The oxalate or salt solution keeps the corpuscles free, and the water lakes the corpuscles and gives a serum.

On a hanging drop slide place one drop of Solution 1 and one drop of Solution 4, the donor's corpuscles and the recipient's serum. The procedure is repeated with Solutions 2 and 3, the donor's serum and the recipient's corpuscles.

These are observed for from twenty to thirty minutes with the microscope or hand lens for clumping. If clumping is marked, this may be seen with the naked eye.

Marble [39] recommends the citrate method. The most important point of technic is that the blood must pass easily and quickly into the citrate solution and be mixed immediately with it before coagulation begins. If known type serums are not available for typing—and they would not be outside of large hospitals—the following method is practical and simple. Blood is drawn from the recipient the same as for a Wassermann test. It is allowed to clot and the serum to separate. The serum is pipetted off and centrifuged until it is clear. Then, 3.8 per cent. sodium citrate solution, in the proportion of 1 part to 10 parts of serum, is added. This mixture is used as a type serum, and is mixed with blood from various donors, rejecting those that agglutinate. Marble calls especial attention to the fact that in the citrate method it is not necessary to cut down on a vein, and he believes that this advantage offsets any disadvantages that the method may possess.

Karsner [40] describes the Lee method of determining blood groups. For this test it is necessary to have the serum of members of Groups II and III. A platinum loopful of each one of these serums is placed on a slide, and to each drop is added either an equal amount of whole blood, or blood placed in 1 per cent. sodium citrate or physiologic solution of sodium chlorid. The reading of the agglutination is made under the microscope, and is usually completed in from five to fifteen minutes. If both drops show agglutination, the blood is in Group I; if neither drop shows agglutination, it is in Group IV; and if one drop shows agglutination and the other does not, it belongs to the group in which there is no agglutination.

The grouping of Lee is as follows:

Cells of Groups	Serums of Groups			
1	—	++*	+++	++++
2	—	—	+	+
3	—	+	—	+
4	—	—	—	—

* The plus sign indicates agglutination or hemolysis.

---

[39] Marble, H. C.: Boston M. & S. J. **182**:153 (Feb. 5) 1920.

[40] Karsner, H. T.: Transfusion with Tested Bloods, J. A. M. A. **70**:769 (March 16) 1918.

According to Lee (quoted by Karsner) the following is the best method of procedure for testing, if serums from known groups are not available.

A small amount of blood is collected from a patient and is allowed to clot. The serum is then obtained. One drop of this serum is placed on a slide and mixed with a drop of a suspension of blood of the donor taken in 1.5 per cent. citrate solution. The reaction will appear in a few moments, and is best examined under the microscope. In the event of a positive reaction, marked agglutination will be evident. The agglutination will also be evident macroscopically.

In the event of a negative reaction, it is a wise precaution to raise the coverglass, and, after making sure that the serum and cells are well mixed, to examine the preparation again. If the test is negative, transfusion may be regarded as being entirely safe.

According to Karsner, from an analysis of a grouping of 1,000 bloods, the chances per thousand bloods of a member of any group having a suitable donor in case the bloods are not tested, are as follows: Group I, 493 bloods; Group II, 886 bloods; Group III, 545 bloods; Group IV, 462 bloods. According to these and other statistics, the chances of any member of whatever group having a successful transfusion if the bloods are not tested is 649 in 1,000.

Drinker and Brittingham,[41] in eighty-three transfusions by the citrate method, noted a rise of temperature of 2 to 3 degrees in 60 per cent. of the cases. The syringe cannula and the paraffined tube methods are much less likely to give reactions than the citrate method. They believe that the plasma is nontoxic, and that one element in the appearance of toxicity is in the platelets, which begin to become abnormal as soon as they leave the blood vessels. Citrated plasma freed from formed elements is nontoxic. The marked whole cell content of blood is uniformly toxic.

It is probable that three elements make up the total of reactions in citrate transfusions: (1) very rare gross incompatibilities; (2) changes in the platelets, part of the process of coagulation, and (3) direct action of the sodium citrate on red cells, promoting hemolysis.

Unger [42] says that the more nearly one uses blood as it exists within the vessels of the donor, the nearer one attains ideal conditions. He is in favor of unmodified blood, and believes that the percentage of severe reactions is much less than when modified (citrated) blood is used. In his series of transfusions with unmodified blood, febrile reactions occurred in only 10 per cent. of all cases as against 60 per cent. of

---

41. Drinker, C. K., and Brittingham, H. H.: Transfusion Reaction, Arch. Int. Med. **23**:133 (Feb.) 1919.

42. Unger, L. J.: Therapeutic Aspect of Blood Transfusion, J. A. M. A. **73**:815 (Sept. 13) 1919.

reactions in Drinker and Brittingham's series with citrated blood. The technic of giving citrated blood is more simple, and this is its chief advantage. Unger reports a professional donor in New York who during six and a half years underwent sixty transfusions, donating thus about 50,000 c.c. of blood. He had lost his total blood volume ten times during this period. His hemoglobin percentage, taken nine weeks after his last transfusion, was 70 per cent., otherwise he was in perfect health.

Unger recommends an average dose of whole blood for infants, of from 80 to 150 c.c.; for adults, from 800 to 1,000 c.c. If overtransfusion takes place, the patient may develop pulmonary edema and die. A short, sharp cough is always a danger sign, and more than 200 c.c. should never be given after this occurs.

Hemophilia is not cured by transfusion, but for the bleeding, transfusion is practically a specific. In purpura hemorrhagica the results are only fairly good, and repeated transfusions are often necessary to control the bleeding. In acute lymphatic leukemia only a temporary favorable effect is secured. In hemorrhagic disease of the new-born, transfusion is specific and often a life saving procedure. In this condition, if hemorrhage from the gastro-intestinal tract occurs, no matter how small it may be, transfusion should be done at once without trying subcutaneous injections of whole blood, which, however, may be effective in hemorrhage from less important sites.

Garbat[43] recommends the citrate method. He collects the blood in two large measuring beakers and then filters it through gauze directly into an infusion flask from which it is allowed to run into the vein of the patient.

In 100 transfusions, 48 per cent. of subjects had no reaction at all, and 10 per cent. had a very slight reaction. A definite reaction occurred in 42 per cent., consisting of chilly sensations or chills, with fever and vomiting in the more severe cases.

A few reactions may be very severe, but do not do permanent harm to the patient. One must be absolutely certain that no clots form in the citrated blood, and to obviate this the mixture of blood and citrate is very thoroughly stirred and then filtered through gauze. If a 0.3 per cent. solution of citrate is used instead of the usual 0.2 per cent. solution, clots are much less likely to form.

---

43. Garbat, A. L.: Sodium Citrate Transfusions, J. A. M. A. **72**:1 (Jan. 4) 1919.

American Journal of Diseases of Children

VOL. 25 MARCH, 1923 NO. 3

THE VALUE OF BASAL METABOLISM IN THE DIAGNOSIS AND TREATMENT OF CRETINISM *

FRITZ B. TALBOT, M.D., AND MARGARET E. MORIARTY

BOSTON

Cretinism was first correlated with endemic goiter by Paracelsus in the sixteenth century. Curling, in 1850, described cases of sporadic cretinism. It was recognized and described as a clinical entity in 1871 by Fagge. In the latter half of the nineteenth century, after the discovery of the cause of myxedema and the part played by thyroid therapy in cases of abnormal glandular secretion, Sir Victor Horsley [1] and Murray,[2] in England, recognized the importance of thyroid administration in cases of cretinism.

In 1895, Magnus-Levy [3] determined the metabolism of adults with exophthalmic goiter and found that it was increased, while in patients with cretinism or myxedema it was much diminished.

In 1909, Bergmann [4] reported the metabolism of a 15 months old infant with severe infantile myxedema and concluded that its metabolism of 790 calories for each square meter of body surface was much diminished. This conclusion holds true when compared with modern standards (the average for the age, according to Benedict and Talbot, being 1,190 calories).

Du Bois,[5] in 1914, reported the basal metabolism of a 36 year old cretin, with a mentality of an 8 year old child, from 18 to 25 per cent. below the normal. After three days of thyroid therapy, he was able to raise the metabolism to normal. In 1916, Talbot [6] found the metab-

---

* Received for publication, Jan. 30, 1923.

* From Children's Medical Department, Massachusetts General Hospital.

* This article is the first of a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

[1] Horsley, Victor: Brit. M. J. **1**:111, 211, 1885.

[2] Murray: Brit. M. J. **2**:798, 1891.

[3] Magnus-Levy: Berl. klin. Wchnschr. **32**:650, 1895.

[4] Bergmann: Ztschr. f. exper. Path. u. Therap. **5**:646, 1909.

[5] Du Bois, E. F.: The Total Energy Requirement of Disease, J. A. M. A. **63**:827 (Sept. 5) 1914.

[6] Talbot, F. B.: Metabolism of a Cretin, Am. J. Dis. Child. **12**:145 (Aug.) 1916.

olism of a cretin, 3⅔ years old, to be 20 per cent. below normal. In 1919, Means and Aub[7] reported metabolic findings on a 20 year old cretin as being 23 per cent. below normal. Recently, H'Doubler[8] found a low basal metabolism in cretins. He was unable, however, to raise the metabolism after grafting a thyroid gland, and concluded that the children were either too old or were not adapted to thyroid grafting.

Fleming[9] has recently made a very important contribution to the study of cretinism and has reported in detail repeated observations on two cretins, one aged 23 months and the other 4 years and 8 months, before and during treatment. He confirmed the earlier observations that the basal metabolism of the untreated cretin is much below normal, and he was able to obtain an increase in the metabolism by the administration of thyroid extract. He showed conclusively that the omission of thyroid therapy results in a fall in the basal metabolism toward its previously low level, with a subsequent rise shortly after treatment was resumed.

Ordinarily, unmistakable signs and symptoms of sporadic cretinism do not manifest themselves until the second half of the first year of life. In the majority of instances, the onset is insidious, and the characteristic physical signs may not appear until the end of the first year, or later.

An explanation for the delay in the appearance of the symptoms is the possibility that up to the time of birth the fetus receives a supply of thyroid secretion through the placental blood which lasts for an indeterminate time and thus delays the appearance of the symptoms. It is not inconceivable that this is supplemented later by small amounts from the mother's milk.

Postmortem findings confirm the well-recognized fact that lack of thyroid secretion is the principle etiologic factor in cretinism, as shown by a complete absence or atrophy of the thyroid gland. While it is admitted that thyroid feeding invariably brings about physical and mental improvement, the physical improvement is nearly always greater than the mental. This lack of complete mental restoration stands out as a therapeutic failure, and stimulates further inquiry into the reasons why a complete cure is not obtained. The question naturally arises whether an early recognition of the disease and improved methods of administering thyroid extract might not result in a more complete restoration of the mental faculties.

The purposes of this communication are, first, to show that determinations of the basal metabolism make possible an early diagnosis of

---

7. Means, J. H., and Aub, J. C.: Basal Metabolism in Hypothyroidism, Arch. Int. Med. **24**:404 (Oct.) 1919.

8. H'Doubler, F. T.: Schweizer. med. Wchnschr. **52**:926, 1922.

9. Fleming, G. B.: Quart. J. Med. **16**:11, 1922.

TABLE 1.—Basal Metabolism of Untreated and Treated Cretins

Case	Age*	Date	Age	Height,* Cm.	Heat Production Each Twenty-Four Hours					Activity	Pulse	Comment
					Weight, Kg.	Total Calories	Calories per Kg.	Calories per Sq. Meter Body Surface				
								Benedict and Talbot	Du Bois			
1. R. T.	♀	4/11/22	23 mo.	....	7.853	393	50.0	937.7	965	I	...	No thyroid; 36 per cent. underweight
		5/25/22	24 mo.	....	8.250	483	58.0	1116	1149	I	...	Thyroid, 1 grain (0.06 gm.) daily
		11/ 2/22	29 mo.	....	10.206	554	54.0	1105	1142	I	94	Thyroid, 1½ grains (0.09 gm.) daily
2. Mc. A.	♀	4/14/22	23 mo.	68.5	8.292	306	30.9	704.6	757	I	...	No thyroid; sitting height, 46 cm.; thyroid, ¾ grain (0.04 gm.) daily, 4/15/22; thyroid, 1½ grains (0.09 gm.) daily, 7/5/22
3. A. DeL.	♀	5/14/21	3 mo.	56.0	4.85	165	34.0	575.5	572	I	106	No thyroid; average 5 periods, 2 days
4. E. S.	♀	6/ 6/21	4½ mo.	....	3.288	193	58.8	866.5	...	II	...	No thyroid; 50 per cent. underweight
		7/25/21	6 mo.	....	3.969	218.8	55.1	895	...	I	...	No thyroid; 55 per cent underweight
		11/22/21	10 mo.	....	5.046	278	55.0	941	...	I	...	No thyroid; 2 periods; 58 per cent. underweight
		12/20/21	11 mo.	....	5.301	342	64.0	1112	...	I	...	Thyroid, 1/10 grain (0.006 gm.) daily; 2 periods.
		3/16/22	13¾ mo.	64.0	6.237	350	56.0	1011	...	I	...	Thyroid, ⅕ grain (0.012 gm.) daily; 2 periods.
		5/23/22	16 mo.	65.0	6.890	668	96.9	1748	1730	II	...	Thyroid, ⅖ grain (0.025 gm.) daily; sitting height, 45 cm.; doing well
		6/19/22	17 mo.	....	6.691	659	98.5	1776	...	I	...	Thyroid, ⅗ grain (0.038 gm.) daily; 34 per cent. underweight; doing well
		9/13/22	21½ mo.	....	7.853	681	86.7	1626	...	II	...	Thyroid, ¾ grain (0.048 gm.) daily; 2 periods
5. E. W.	♀	10/31/22	10 mo.	77.0	9.27	578	62.3	1234	...	I	...	Treated from 3 mo. on; now getting 3 grains (0.2 gm.) daily; average of 2 periods
6. J. P.	♀	5/11/22	5½ yr.	82.5	13.750	394.6	28.7	636.5	...	I	...	No thyroid; average 2 periods
		6/ 8/22	5½ yr.	....	12.984	576.3	44.4	965	...	I	...	Receiving thyroid, 1 grain (0.065 gm.) daily for ten days
		11/ 5/22	6 yr.	....	13.580	847.3	62.4	1380	...	II†	110	Receiving thyroid, 1 grain (0.065 gm.) daily
7. W. G.	♂	11/18/19	10 yr.	120.0	24.5	811	33.0	858.2	902†	I	76	Varying amounts of thyroid off and on from 1 year of age on
		12/ 6/19	10 yr.	120.0	25.5	784	30.8	796.8	858†	I	76	Varying amounts of thyroid
		12/30/19	10 yr.	120.0	24.5	907	37.0	959.8	1008†	I	80	Varying amounts of thyroid
		5/16/20	10½ yr.	120.0	24.0	854	35.6	916.3	955†	I	76	No thyroid for 2 weeks
		12/ 9/21	12 yr.	126.5	26.0	1118	43.0	1108	1165†	I	81	Thyroid, 4½ to 7½ grains (0.58 to 0.78 gm.) daily
		6/ 2/22	12½ yr.	129.0	28.5	{736.8 {696	{25.9 {24.4	..... 650.9	729† ...	I I	56} 56}	No thyroid for 3 months
		12/ 1/22	13 yr.	130.5	28.92	859	29.7	796	...	I	...	Thyroid irregularly
8. M. S.	♀	11/28/22	26 mo.	67.2	7.88	245	31.0	582.9	608	I	...	No thyroid; average 3 periods
§9. C. G.	♂	1/19/15	3 yr., 8 mo.	85.0	11.83	479	40.5	902	898‡	I	95	No thyroid; average 2 periods
10. M. M.	♀	11/24/22	5 yr.	92.2	17.27	{634 {549	{36.7 {31.8	{878.0 {709.2	{993.6 {859.9	I, awak 1, aslee	...	No thyroid, 1 period
		12/ 7/22	5 yr.	92.0	16.42	787.7	48.0	1128	1125	I-II	96	Thyroid, 1 grain (0.065 gm.) daily; average 2 periods

* In this column ♀ represents female and ♂ represents male.
† Portable apparatus used through the kindness of Dr. J. H. Means; body surface determined by DuBois height-weight chart.
‡ Lissauer.
§ Previously reported, Footnote 6.

cretinism before the usual clinical symptoms appear; second, to show the correct standard to use in childhood in determining whether a subject is suffering from hypothyroidism or not, and third, to show that determinations of the basal metabolism are of distinct value in indicating the amount of thyroid which may be given with maximum efficiency.

The growth of the infant's brain is very rapid, and, at the end of the first year, it is two and one-half times the original size. This is also the period of greatest proportional growth of the rest of the body. If the failure to obtain complete mental restoration can be traced to the absence of thyroid secretion during this period of rapid growth and if the thyroid gland supplies a necessary substance for complete development of the brain cells, then the importance of an early recognition of cretinism cannot be overemphasized.

Table 1 shows the basal metabolism findings in a series of ten cretins, including one case previously reported,[6] all of whom were studied in the respiration chamber at the Massachusetts General Hospital.

TABLE 2.—Comparison of Weight and Basal Metabolism of Untreated Cretins with Those of Normal Children

Case	Age	Age According to Weight	Age According to Basal Metabolism
1. R. T.	23 mo.	8-9 mo.	5-6 mo.
2. McA.	23 mo.	8-9 mo.	4 mo.
3. A. DeL.	3 mo.	3 mo.	New-born infant
4. E. S.	4½ mo.	Birth	New born infant
	6 mo.	1 mo.	1 mo.
	10 mo.	3 mo.	3 mo.
6. J. P.	6 yr.	2½ yr.	6-7 mo.
7. W. G.	12½ yr.	11 yr.	4 yr.
8. M. S.	26 mo.	8-9 mo.	2 mo.
9. O. G.	3 yr., 8 mo.	23 mo.	10 mo.
10. M. M.	5 yr.	4½ yr.	2 yr.

With the exception of Case 5 in which the patient had received thyroid from the age of 3 months and Case 3 in which the patient came under observation at the age of 3 months before thyroid deficiency had an opportunity to affect the growth in weight and stature, all the patients in this series were shorter and weighed less than normal infants of the same age. The proportion of their weight to their height was within normal limits; but the distribution of the weight was quite different from that of normal children, as shown by measurements, the trunk and abdomen being proportionately heavier than the extremities.

A study of Table 2 reveals that the weight and basal metabolism of these untreated cretins fall very much below those usually seen in normal children. It also gives an indication of the age development of the untreated cretins of this series.

Table 2 reveals that the basal metabolism and physical development of a cretin before treatment are considerably lower than they should be, and illustrates the importance of the thyroid gland as a growth-promoting factor.

In the accompanying charts, the metabolism of the untreated and treated cretins has been plotted for comparison with the normal, showing the heat production for each square meter of body surface, total calories referred to weight, and total calories with reference to age.

Chart 1 shows the heat production for each unit of body surface of untreated and treated cretins in relation to the normal metabolism.

The low distribution of the solid dots and crosses (untreated cretins) conforms in general to the results of metabolic studies on adult cretins (the metabolism of abnormal adults is usually compared with the normal heat production for each square meter of body surface). Some of the cases in this series fall so close to the normal limits that if the basal metabolism for each unit of body surface was the sole criterion used, a diagnosis of cretinism would not be justified. On the other hand, in seven instances, the metabolism was extraordinarily low.

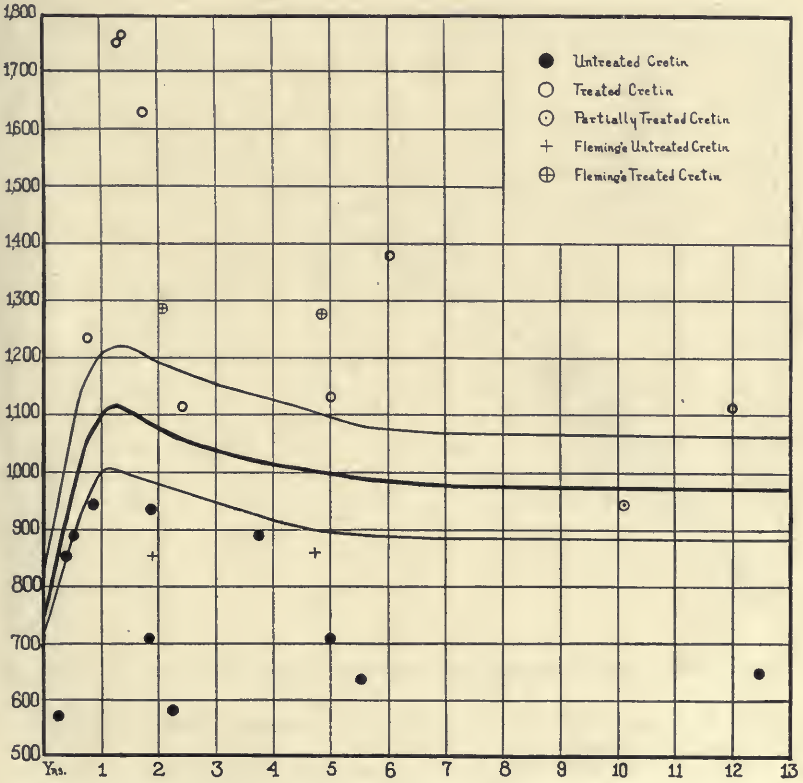


Chart 1.—Basal metabolism of treated and untreated cretins: calories for each square meter with reference to age. The meaning of the symbols is the same in all of the charts.

A comparison of the metabolism of the treated cretins with the average curve for each unit of body surface is very misleading and presents a picture which would lead one to suppose that they were cases of hyperthyroidism. Consequently, a comparison with the normal heat production for each unit of body surface may convey an erroneous impression; the heat production for each kilogram of body weight is even of less value. Since careful and numerous measurements of the body were made according to the Du Bois linear formula, the measurements of the body surface are as accurate as possible, without directly measuring the surface area.

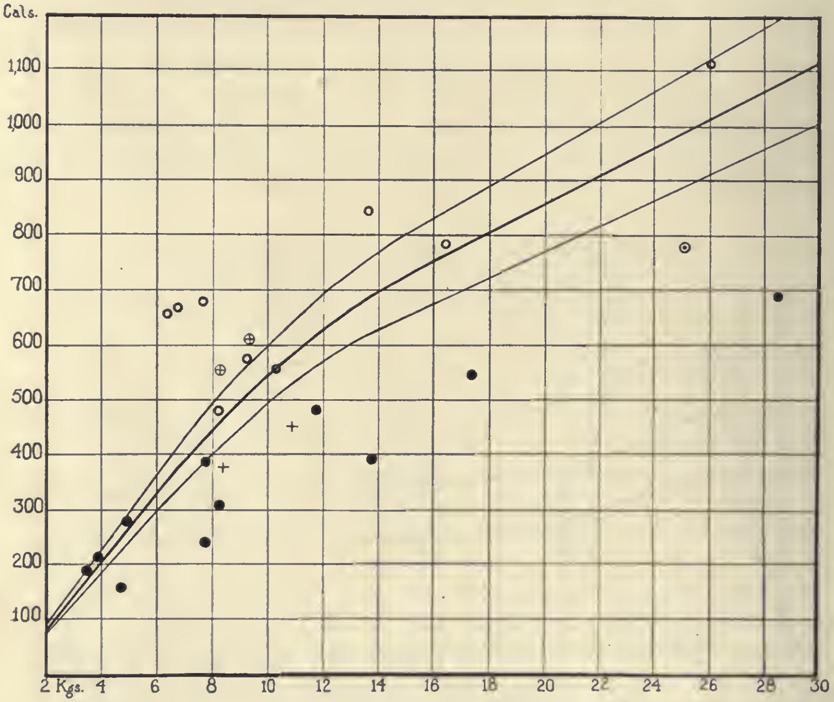


Chart 2.—Basal metabolism of treated and untreated cretins: total calories with reference to weight.

A comparison of the total heat production with reference to the weight and age gives a better picture of the relation of untreated and treated cases to the normal. Chart 2 shows a comparison of the total heat production of the untreated and treated cretins with reference to weight in relation to the normal curve.

The metabolism with reference to weight of the untreated cretins, with two exceptions (Cases 1 and 4), falls below the normal limits, and that of the treated cases rises above the normal in most instances. On this chart, there is a much more equal distribution of the cases than there is when they are compared on the basis of body surface. The findings are about what one would naturally expect, since with thyroid therapy there is a loss of inactive myxedematous tissue and a marked rise in the metabolism toward normal.

One patient (Case 4) was suffering from malnutrition. The expected metabolism for her weight is consequently higher than the normal. Compared with that of infants with the same degree of malnutrition without evidence of deficient thyroid, her metabolism was low. It was necessary in this case to give enough thyroid to bring the metabolism up to that which might be expected in a patient with the degree of malnutrition that she exhibited. The metabolism will probably remain above the standard for the weight until a gain in weight removes her from this classification. The height reached by the metabolism after treatment is well shown in Charts 1 and 2.

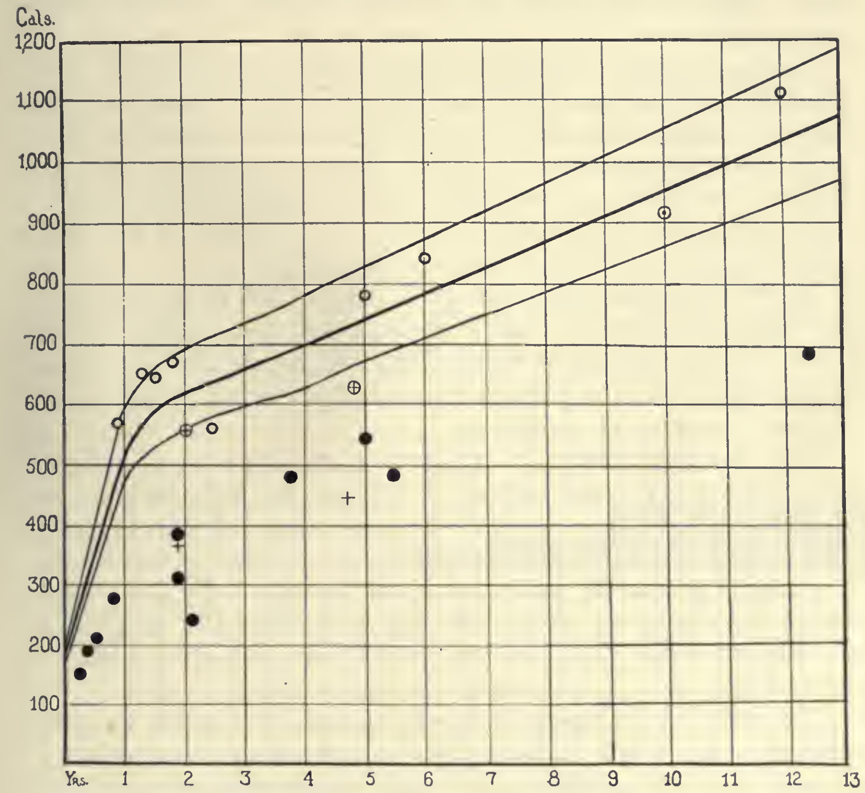


Chart 3.—Basal metabolism of treated and untreated cretins: total calories with reference to age.

The total metabolism of untreated cretins for each twenty-four hours, plotted to the normal curve for the age, reveals a more regular distribution of dots than on any of the other charts.

In the majority of cases studied, the most marked clinical improvement was not obtained until enough thyroid had been given to raise the metabolism to the expected metabolism for the age.

Two treated cases in Chart 3 fall below the 10 per cent. variation, and the question might very well be raised as to whether these patients were receiving a sufficient amount of thyroid. The dose has been increased with benefit; but the level of the metabolism has not been determined. The difficulty of obtaining basal periods after treatment had been started was encountered in several instances and explains the lack of data after treatment in some cases. Fleming also encountered the same difficulty.

The growth factor is probably the main cause of difference in the metabolism of childhood and adult life, and, as a consequence, age plays an important part in the interpretation of results. Chart 3 demonstrates that the metabolism of cretins is greatly retarded for their age. The low distribution of the dots of the untreated cretins shows a certain uniformity and suggests that it may be possible to predict the metabolism of an untreated cretin of a given age.

Since the purpose of treatment in cretins is to bring them up to the average normal for the age, it seemed wise to give sufficient thyroid to bring the metabolism to the expected total metabolism for the age. The evidence to date is that this level must be reached before the best therapeutic results can be obtained.

Basal metabolic studies are of distinct therapeutic value as an indication of the correct dosage of thyroid. This is very well shown in Case 5 of this series (E.W.), in which the patient was first seen at the age of 8 months, after receiving small doses of thyroid for five months. The amount of thyroid was increased to 3 grains (0.195 gm.) a day, and at 11 months her metabolism was determined and found to be normal for the age. This, with her clinical improvement, was taken to indicate that she was receiving the optimum dose.

The effect of overdosage of thyroid has been reported in an earlier publication,[6] in a case of myxedema in which excessive amounts of thyroid were given, resulting in a very high metabolism (+ 70 per cent.) and untoward symptoms. This could have been obviated if more attention had been paid to the advice given on the basis of the metabolism reports.

Du Bois was able to bring the metabolism of an adult cretin, in a few days, up to normal. In an infant, however, the growing organism is more delicate, and it is better to work up to the normal more slowly. In cases with questionable deficiency of thyroid secretion, basal metabolic studies are also a great help. When the metabolism is normal in these cases, thyroid treatment is distinctly contraindicated. Many such cases have come under observation.

Case 7 of this series is an example of variations in the metabolism, due to the intermittent administration of thyroid. If it had been possible to make occasional determinations of the basal metabolism in this case, from birth on, in order to regulate the thyroid treatment, much better results might have been obtained.

The earlier the diagnosis of cretinism is made, the earlier the treatment may be instituted. Case 4, reported herewith, illustrates the value of basal metabolic determinations in making an early diagnosis of cretinism. The patient was first seen at 3½ months, at which time she had a thickened tongue, slightly hoarse voice, and a suggestion of supraclavicular fat pads. The hair was neither coarse nor fine. The signs were so indefinite that the opinion of several pediatricians was equally divided as to whether or not she was a cretin. Since there was considerable clinical doubt, and, although her basal metabolism determined at 4½ months, indicated hypothyroidism, no treatment was given; but studies of her metabolism were made at intervals up to 10 months of age. This case was allowed to progress without treatment for several months in order to prove to our own satisfaction that a diagnosis of cretinism could be made as early as 3 months of age. The signs were so indefinite in the early months that a clinical diagnosis at this time might have been questioned; but at 10 months, when treatment was instituted, there was no question about the clinical diagnosis. This indicates that a very early diagnosis of cretinism may be made by means of the respiratory chamber. Thyroid therapy was then begun, and the effect upon the metabolism is shown in Chart 4.

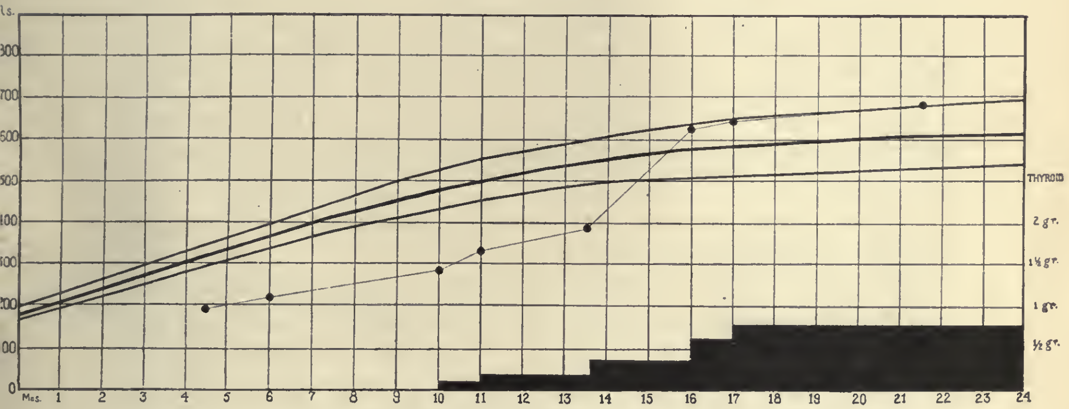


Chart 4.—Basal metabolism in Case 4, showing the effect of the administration of thyroid on the heat production: total calories with reference to age.

When she received ⅗ grain (0.038 gm.) of thyroid a day, her metabolism reached that expected for her age. Rapid progress, both mental and physical, was noted. This case indicates that a definite diagnosis of hypothyroidism may be made very early, with the aid of the respiratory chamber, in cases in which a definite clinical diagnosis is not possible. Early institution of treatment is thus made possible, and, as a consequence, better results may be obtained in the future. Records of the end-results of treatment instituted in the second or third months are not available, and it remains for the future to show whether such treatment will result in both normal bodies and normal minds.

With the increasing interest in studies of the basal metabolism as an aid in the diagnosis and treatment of cases of deficient glandular secretion, too much emphasis cannot be laid on the correct interpretation of results. The greatest difficulties are encountered in childhood because of the change of standards due to growth. This note of warning is sounded against the drawing of too hasty conclusions without due deliberation and sufficiently accurate evidence.

CONCLUSIONS

1. The metabolism of a cretin is low compared to that of a normal child.
2. It is possible to differentiate, by means of basal metabolic determinations, between questionable hypothyroidism, cretinism and normality.
3. The dosage may be regulated by the laboratory findings and kept at the most efficient dose.
4. Present evidence indicates that the total metabolism should be raised to the expected metabolism of normal children of the same age.
5. Basal metabolic studies make a diagnosis of cretinism possible as early as 3 months of age. Better results should be obtained if treatment is started in the early months and persisted in.

REPORT OF CASES

Case 1.—R. T., girl, aged 22 months, the ninth child, whose birth was normal and who had always been considered slow in development, both mentally and physically, came under observation in March, 1922. She had not walked, talked or played. She knew her name and recognized her mother's voice. The mother thought that the child was shorter than she should be. The baby kept its mouth open and curled its tongue out and downward. The tongue had always been large. The child did not perspire, and its skin had always been scaly. The child had always been constipated.

The child was fairly well developed and nourished. The fontanel was still patent and measured 4 by 3 cm. The bridge of the nose was flat. The mouth was open, and the tongue was thick and protruded most of the time. There were noticeable fat pads above the clavicles. The arms and legs were short; the hands, fat and square. The abdomen was protuberant, and there was a marked umbilical hernia. The skin was dry; the feet were cold, and the hair was slightly coarse. Otherwise, the physical examination was negative. The child presented the characteristic picture of cretinism.

During the following six months, the child was given 1 grain (0.06 gm.) of thyroid, daily. She commenced to walk and talk, and the mental condition began to improve. Basal metabolism determination revealed that not enough thyroid had been given. Consequently, the dose was increased to 1½ grains (0.09 gm.) a day, after which there was marked improvement.

Case 2.—McA., girl, aged 22 months, was normal at birth and had exhibited no abnormal characteristics until between the eighth and twelfth months, when the parents became worried because the child did not sit up or hold anything in its hands.

The hair was sparse and coarse, and the skin was yellowish and dry. The bridge of the nose was flat; the voice was hoarse, and the tongue was large and protuberant. The child had no teeth. There were marked supraclavicular fat pads. The abdomen was large, and there was a noticeable umbilical hernia. The arms and legs were short. The child presented the characteristic picture of cretinism.

Thyroid was given, and the doses were increased up to 1½ grains (0.09 gm.) a day. Attempts to obtain the basal metabolism after treatment were impossible because the child was so active.

Case 3.—A. DeL., girl, who was normal at birth, at 2 months became constipated. This increased to such an extent that she had a bowel movement only once in three days. The feet were always cold, and the mother thought that the child's cry was different from that of other babies.

Physical examination revealed poor capillary circulation. The skin was dry, rough and yellowish. The nose was rather flat; the nostrils broad, and the tongue large. The hair was abundant and quite coarse. The eyelids were heavy, and the mouth was held open. There was a moderate sized umbilical hernia.

A diagnosis of cretinism was made, based both on the clinical findings and on the low basal metabolism determination. Unfortunately, this child died a short time later of bronchopneumonia, before it was possible to bring the metabolism up to normal.

Case 4.—E. S., girl, was first seen at the age of 3½ months. She had been breast fed since birth. At birth she weighed 6½ pounds (2.9 kg.); at 3½ months she weighed 7 pounds and 6 ounces (3.3 kg.). She had always been constipated. The history was negative except that she had not gained in weight.

Physical examination revealed a small, poorly nourished infant. The skin was mottled and red. The fontanel was open and level, and measured 2 by 2 cm. There were large rolls of fat under the chin, and pads of fat above the clavicles. The hair was fine and silklike. The facial expression was suggestive of cretinism. Of five members of the visiting staff of the hospital who saw her at this time, three believed that she was a cretin and two thought she was not. The voice was a little hoarser than it should have been. This seemed to be the evidence in favor of cretinism and the factor on which most stress was laid. The basal metabolism was low. She was kept under continuous observation. Two and one-half months later, the tongue was growing larger, and she had not gained in weight. She was very much constipated and continued to keep her mouth open. Examination at 10 months of age revealed an extremely thick tongue, which was so large that it was impossible to look down her throat. The cheeks were thick and pudgy; the nose was flat, and the voice was hoarse. The trunk was relatively large and the extremities short. It was possible to make, at this time, a definite diagnosis of cretinism.

Thyroid therapy was then instituted, and there was a marked improvement in the general condition. The dose of thyroid was eventually increased to ¾ grain (0.048 gm.) a day. When last seen, she looked very much better; but the musculature was still somewhat flabby. The tongue was still large, but smaller than it was at the time of the previous examination. She is still under observation.

Case 5.—E. W., girl, aged 7 months, was seen because she had a large, thick tongue and was not gaining rapidly in intelligence.

Physical examination revealed a well developed and well nourished child. The tongue protruded most of the time. The hair and voice were normal. She perspired when she cried. There were moderate sized fat pads above the clavicles, but no other evidence of cretinism. A diagnosis of cretinism was first made in this case when the patient was 3 months old. She had been given thyroid from that time on, at first in small amounts, ¾ grain (0.04 gm.), a day. The amount of thyroid was then increased slowly up to 3 grains (0.19 gm.) a day. The question then arose as to whether or not she had received enough thyroid. The basal metabolism was within normal limits. The last report from the parents was to the effect that the child was improving.

Case 6.—J. P., girl, aged 5 years, came under observation with a diagnosis of cretinism. There was no history of constipation. The appetite had been very irregular. At 5 years she talked like a 2 year old child, and was very quiet and "lazy."

Physical examination revealed a pale, apathetic, obese child, with a stocky, heavy trunk, short feet and hands. The face and limbs looked edematous. The subcutaneous fat was firm and indurated. There were large, pudgy fat pads in the supraclavicular fossae. The child had a double chin. The hands were square. The skin was extremely dry and wrinkled in various parts and appeared yellowish. The hair was dry and coarse. The scalp was dry and scaly. The teeth were carious. The tongue was much enlarged. The bridge of the nose was depressed. She presented a characteristic picture of cretinism.

The administration of thyroid extract was commenced, followed by considerable improvement. It was difficult to increase the thyroid above ¼ grain (0.016 gm.) a day without upsetting her. The basal metabolism determination, however, revealed that she was not receiving enough thyroid to give the most efficient results. Attempts are now being made to increase the dose.

Case 7.—W. G., boy, was first seen at the age of 1 year because he was "stupid" and would sit for days without laughing or crying.

Physical examination revealed a square head, very hoarse voice, coarse, sparse hair and fat extremities, which were short in relation to the trunk. The skin was dry and rough, and there were very marked supraclavicular fat pads. The tongue was large and thick. The abdomen was normal but fat, and there was a large umbilical hernia. Thyroid therapy was commenced and given in varying amounts. The mother would give thyroid for a certain time and then would stop giving it when the supply was exhausted. When the child would seem stupid, she would return to the hospital and obtain more thyroid.

The metabolism, at the age of 10 years, was obtained by Dr. J. H. Means in the portable apparatus. Because of the varying amounts of thyroid which were given, the metabolism varied from considerably below normal to normal, at different periods in which the child was under observation. This case shows that thyroid therapy must be continuously administered in order that results may be obtained.

Case 8.—M. S., girl, came under observation at the age of 26 months because she was backward and had not developed normally. When first seen, she presented a characteristic picture of cretinism, with a flat nose, dry skin, with a yellowish tinge, coarse dry hair, large tongue, supraclavicular fat pads, disproportion of the body, umbilical hernia and hoarse voice. The basal metabolism was determined before thyroid was given.

Case 9 was reported[6] previously.

Case 10.—M. M., girl, had an uneventful history during infancy. The first tooth was cut at 10 months, and the child walked at 20 months. Nothing out of the way was observed until she was 2 years old, when the mother thought that the baby was not developing as fast as she should. When seen she presented the characteristic appearance of a cretin. The hair was sparse and coarse; there was seborrhea of the scalp; the nose was flat and broad; the tongue was large; the voice, hoarse, and the complexion pale and yellowish.

The skin was dry and coarse over the entire body. The extremities were relatively short compared with the trunk. The hands were square and spadelike. There were marked supraclavicular fat pads and a large umbilical hernia. The abdomen was large. There was much myxedematous tissue, with relatively little musculature. After thyroid therapy was begun, the child lost 1 kilogram in a month. The greater part of this loss in weight was in the trunk and abdomen, and the fat pads had in part disappeared. After three weeks during which she was given 1 grain (0.06 gm.) of thyroid a day, some supraclavicular fat pads remained; the tongue was somewhat smaller; the voice was not particularly hoarse, and the hair was falling out. There was obviously an increase in intelligence. The eyes were dry, and she took more interest in her surroundings. A healthy pink color appeared, and the yellowish tint of the skin had disappeared.

THE BACTERIOLOGY OF THE URINE IN ACUTE NEPHRITIS IN CHILDREN *

LEWIS WEBB HILL, M.D., EMILY F. HUNT, A.M.
AND
ELSIE W. BROWN, A.B.
BOSTON

Most cases of acute nephritis in children follow, or occur coincidentally with, some acute infection elsewhere in the body, tonsillitis being, in our experience, the most frequent one encountered. The question naturally arises whether the kidney condition is produced by bacteria which have gained access to the blood from the throat or from some other locus of infection, and thence invade the kidney, or whether a soluble toxin excreted through the kidney is responsible for the trouble.

As far as we know, no systematic study of the question has been made, as regards children, although a number of observations are on record for adults. Inasmuch as the type of case studied in adults by other observers has been, for the most part, widely different from acute nephritis as we see it in children, no conclusions can be drawn by comparing our results with theirs. Therefore, a review of these observations would be of no particular value here. Some observers have isolated bacteria from the urine of adults with acute, subacute or chronic nephritis, while others have failed to do so. All sorts of bacteria have been isolated, from streptococci of various sorts to diphtheroids and "small gram-negative anaerobic bacilli." There has been no uniformity in results, which is not to be wondered at when one considers the widely different types of cases that have been studied. Some observers have included in their series cases of ulcerative endocarditis with embolic foci in the kidneys, as well as cases of subacute or chronic nephritis in which no infectious agent is apparent.

The common form of acute nephritis as it occurs in children offers an especially good field for study, as almost all the cases seen are very much the same, and, in our series, no cases have been included in which there was any indication of septicemia, cardiac infection or purpura. The cases studied were all of the ordinary type, coming on in some instances without apparent cause, but usually secondary to tonsillitis or other infections in the nose, throat, ears or cervical glands.

---

* Received for publication, Dec. 12, 1922.

* From the Medical Service, Children's Hospital, and the Department of Bacteriology, Harvard Medical School.

Twenty-one cases were studied. In every instance, the disease was in the acute stage, that is, the urine showed large amounts of blood, in almost all cases macroscopically. Cultures of the urine were obtained from three days to a month after the onset of the disease; in about 50 per cent. of the cases, within a week after the onset. It would have been much better, of course, to obtain the urine the day of onset; but this was obviously impossible, as all the cases were hospital patients who had not entered until they had been sick for several days. In addition to the urine cultures, the leukocyte count and the temperature were studied in connection with the question of infection.[1]

TECHNIC OF URINE CULTURES

The penis or the vulva was carefully washed with soap and water, followed by boric acid solution, and the urine obtained by catheterization with a sterile catheter. In only two cases was there any question of contamination.

Cultures from the urine specimens were started immediately after the specimens had reached the laboratory. Throughout all attendant manipulations, aseptic precautions were taken.

The urine was transferred to sterile centrifuge tubes and centrifugalized for twenty minutes at a fairly high speed. Direct smears were made and stained by the Gram and Ziehl-Neelson methods. The supernatant fluid was then withdrawn, and the sediment planted on plain agar slants, blood serum slants, Endo's agar plates and blood agar plates.[2]

Reports were made after the cultures had been incubated for forty-eight hours; but the apparently sterile cultures were kept for at least four days to give slow-growing organisms a chance to develop. No organisms of this type were found, however.

This technic, we believe, is sufficient to permit the growth of all ordinary organisms. The results are recorded in the accompanying table.

COMMENT

In sixteen cases, the urine was sterile. In two cases, *Staphylococcus albus* was found (probably a contamination), a diphtheroid bacillus in one (unaccounted for), and colon bacilli in two. The cases which showed colon bacilli had high leukocyte counts (17,800 and 29,000), with a good deal of pus in the urine, as well as blood and casts, due probably to a complicating pyelitis.

---

[1] These examinations were made by the house officers as a part of the routine entrance examination.

[2] The culture mediums used were: Endo's agar; Loeffler's blood serum; nutrient veal infusion broth (plus 0.5 to phenolphthalein); blood agar: nutrient beef infusion agar (plus 5 per cent. horse blood); agar, titrated (plus 0.5 to phenolphthalein).

Only two patients showed fever during the course of the disease, although it is possible and probable that in many cases fever was present at the onset, before the child entered the hospital. One of these patients had cervical adenitis, which accounted for the fever. One had a complicating pyelitis. The leukocyte count was elevated (over 12,000) in six cases. In three of these, this was accounted for by the presence of acute cervical adenitis. In two others, it was accounted for by a complicating pyelitis. In one case a leukocyte count of 19,800 was unaccounted for.

Results Obtained in Twenty-One Cases

Case	Patient	Duration	Apparent Etiology	Leukocytes	Urine Cultures	Comment
1	H. C.	7 days	Cervical adenitis	14,400	Staphylococcus albus (2 cultures)	Swollen glands in neck probably the cause of high leukocyte count
2	D. N.	14 days	Tonsillitis	9.400	Sterile	
3	P. G.	10 days	Tonsillitis	9,400	Sterile	
4	T. J.	14 days	Tonsillitis	11,600	Sterile	
5	L. B.	4 days	Cervical adenitis	15,500	Sterile	Temperature 104 F. at entrance, caused by swollen glands in neck; probably accounting for high leukocyte count.
6	S. W.	6 days	Impetigo	10,900	Sterile	
7	A. G.	7 days	? ?	18,000	Staphylococcus albus	No fever
8	G. W.	7 days	Impetigo	12,600	Sterile	Urine unusually bloody
9	A. McG.	1 month	Tonsillitis	8,400	Sterile	Very severe case, with much edema; patient died
10	C. K.	12 days	Tonsillitis	12,800	Sterile	
11	R. W.	7 days	Pneumonia	14,600	Sterile	
12	A. DeA.	1 month	Tonsillitis	19,800	Sterile	
13	E. S.	8 days	? ?	12,400	Sterile	
14	J. C.	6 weeks	? ?	10,000	Sterile	
15	D. C.	14 days	? ?	6,400	Diphtheroid	
16	S. J.	14 days	Tonsillitis	17,800	Colon bacillus	A good deal of pus in urine; probably had a complicating pyelitis
17	F. W.	7 days	? ?	4,700	Sterile	
18	P. Q.	7 days	? ?	10.300	Sterile	
19	C. F.	4 days	? ?	18,400 to 29,000	Colon bacillus	High fever continually, and general symptoms of infection; urine very bloody, containing also considerable pus; probably a colon infection of the kidney
20	L. H.	6 days	Tonsillitis	25,000 to 14,000	Sterile	High leukocyte count accounted for by coincident cervical adenitis; fever at entrance
21	M. D.	3 days	Tonsillitis	5,800	Sterile	

These results indicate that in most cases of acute nephritis in children, after the disease has once been established, there are no bacteria demonstrable in the urine, and there are probably none in the kidney. There is no fever, no elevation of the leukocyte count, in short, there is probably no bacterial infection of the kidney present during the course of the disease. However, these results do not rule out the possibility of bacterial infection of the kidney at the very onset of the disease, and, indeed, this is a very strong possibility, which is suggested by the work of Pappenheimer, Hyman, and Zeman,[3] who injected bacteria directly into the renal artery of rabbits. They found that the bacteria were taken up by polymorphonuclear and endothelial cells in the glomeruli within a few minutes, and that, within four hours, they had nearly all undergone complete intracellular digestion. They believe that the toxins liberated by the rapid lysis of the bacteria within the glomerulus are the cause of the injury which is produced. This hypothesis is also borne out by clinical observation on children with acute nephritis at the very onset of the disease, for, in the few cases which we have seen in private practice in this early stage, there has always been a sharp and sudden rise in temperature coincident with the appearance of bloody urine, which usually subsides in about forty-eight hours.

The other possibility is that not bacteria, but soluble toxins absorbed from the infected focus (tonsils, cervical glands, etc.) produce the injury to the glomeruli.

CONCLUSIONS

1. In the ordinary type of acute nephritis in children, there is probably no continued growth of bacteria within the kidney during the course of the disease.

2. It is possible that bacteria may be the cause of the condition, however, and that they produce the characteristic injury to the glomeruli during the very early stages, and then soon die out.

3. It is also possible that soluble toxins, and not bacteria, may be the cause of the disease.

---

[3] Pappenheimer, Hyman and Zeman: Proc. New York Path. Soc. **16**:73, 1916.

INTRAPERITONEAL TRANSFUSION WITH CITRATED BLOOD *

A CLINICAL STUDY

DAVID M. SIPERSTEIN, M.A., M.D.
Senior Resident in Pediatrics, Minneapolis General Hospital
MINNEAPOLIS

In a previous paper [1] an attempt was made to show, by means of experimental data that the intraperitoneal transfusion of freshly citrated blood is a method of distinct value. It was found that it was a safe procedure, simple in its application and clinically effective. It was proposed as a therapeutic procedure of merit in selected cases. It is the purpose of the present paper to report in some detail five cases in which the intraperitoneal route for blood transfusion was utilized.

REVIEW OF LITERATURE

The intraperitoneal injection of defibrinated blood was first used clinically by Ponfick [2] in 1875. Isolated cases have been reported by Golgi and Raggi,[3] Magniagalli,[4] Scottini,[5] Giovanni,[6] von Kaczorowski,[7] Liegl [8] and Burresi.[9]

Careful observations and laboratory data were not given in any of the cases cited. In all instances, defibrinated blood was used. The results obtained were extremely variable and, for the most part, unsatisfactory.

---

* Received for publication, Nov. 15, 1922.

* From the Departments of Pharmacology and of Pediatrics, University of Minnesota.

[1] Siperstein, D. M., and Sansby, J. M.: Intraperitoneal Transfusion with Citrated Blood, An Experimental Study, Am. J. Dis. Child. **25**:107 (Feb.) 1923.

[2] Ponfick: Experimentelle Beiträge zur Lehre von der Transfusion, Virchows Arch. f. path. Anat. **62**:273-275 (Jan. 20) 1875.

[3] Golgi and Raggi: Trasfusione di sangue nel peritonéo in un alienato oligocitemico, Gazz. med. ital. **7**:61 (Feb.) 1880.

[4] Magniagalli: Peritoneale Bluttransfusion, Zentralbl. f. Gynäk. **19**:463 (Sept. 11) 1880.

[5] Scottini, Pietro: Trasfusione di sangue nel peritonéo in una donna malata di grave anemia per anchilostomia, abstr. Jahresb. d. med. Wiss. **16**: 1,304, 1881.

[6] Giovanni, A. de: Un caso di gravissima anemia felicemente mediante la transfusione di sangue intraperitoneale, abstr. Jahresb. d. ges. Med. **16**: 240, 1881.

[7] Von Kaczorowski, Fünf Fälle von Bluttransfusion in die Peritonealhöhle, Deutsch. med. Wchnschr. **6**:610, 1880.

[8] Liegl: Ueber peritoneale Transfusion, Aerztl. Intelligenzbl., München, No. 4, Jan. 22, 1884.

[9] Burresi, P.: Trasfusione sanguigna peritoneale in uno caso di anemia perniciosa, abstr. Jahresb. d. ges. Med. **18**:256, 1883.

In an exhaustive search through the available literature, I have been unable to find any reports on the clinical use of the intraperitoneal route for transfusions since 1884. So far as I know, citrated blood has never been given intra-abdominally.

MATERIAL AND METHODS

The clinical diagnoses in the cases herewith reported were: Case 1, secondary anemia; Case 2, congenital syphilis; Case 3, dehydration, decomposition; Case 4, hemolytic anemia, hemoglobinuria (obscure origin); Case 5, secondary anemia.

Patients are not allowed to have any breakfast on the day of the transfusion. No other preliminary precautions are taken. A freshly prepared 2 per cent. solution of sodium citrate is used in the proportion of 10 c.c. of solution to every hundred c.c. of donor's blood. Both recipient and donor are grouped before each transfusion. It is needless to mention that strict aseptic precautions are taken. The donor's blood is strained through gauze, and then immediately injected into the peritoneal cavity of the recipient.

Details regarding amounts transfused and results obtained are given in the protocols and in the charts.

Hemoglobin estimations, red blood cell counts, and smears were taken in several cases at hourly intervals following each transfusion. Hemoglobin determinations were made with the Fleischl-Miescher hemoglobinometer.

On the day of transfusion all urine and feces specimens were examined for occult blood. Thereafter, daily specimens were tested for positive reactions. The benzidin and guaiac tests were used.

The work here reported was done under the most favorable conditions possible at the Minneapolis General Hospital, with the assistance and complete cooperation of the nurses and the laboratory staff.

REPORT OF CASES

Case 1.—*Secondary anemia. History.*—A boy, aged 2 years, American, was brought to the service of Dr. E. J. Huenekens, at the Minneapolis General Hospital, Aug. 22, 1922. Poor appetite, weakness and pallor had been noted since birth. The family history was negative. The mother had deserted the child one week before admission. Birth was normal and occurred at term. The child was breast fed for two weeks; then he was fed on a cow's milk mixture (not under a physician's care). He apparently developed normally and walked at 15 months. He had pertussis and measles at 12 months with no sequels. He had always been a weak and frail child. The history by systems was entirely negative. The weight on entrance was 22 pounds (10 kg.).

Physical Examination.—The temperature was 100.4 F.; pulse, 110. The patient was in bed and looked very anemic. His development was good; but nutrition was poor. He was depressed. There was no edema, cyanosis or jaundice. The head was square; the fontanels were closed; the frontal bosses were prominent. Examination of the eyes, ears, nose and throat and of the heart and lungs was negative. The anterior cervical and submaxillary nodes

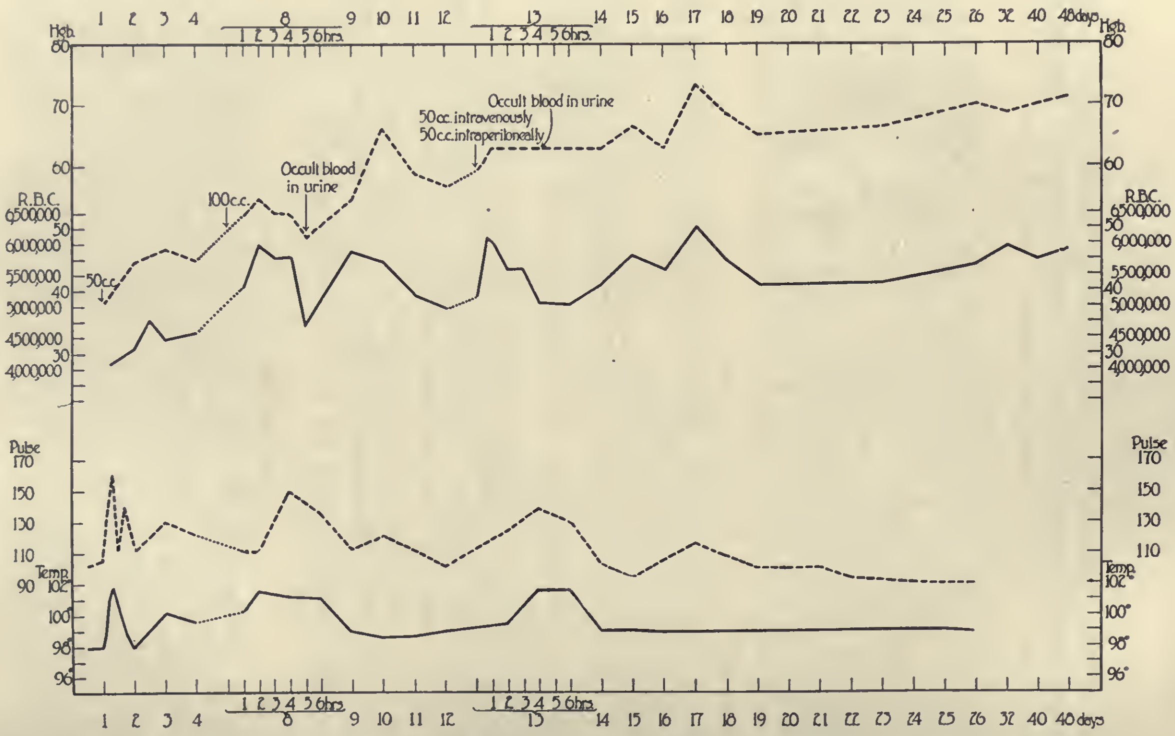


Fig. 1.—Graphic presentation of Table 1 (Case 1), showing temperature and pulse reactions.

were palpable. The patient was "pot-bellied." The spleen was palpable, 2 cm. below the costal margin, in the midclavicular line. The liver was palpable, 3 cm. below the costal margin. Both upper and lower extremities were negative, except for marked anemia of the upper.

Laboratory Findings on Admission.—The urine was amber and was acid in reaction, and the specific gravity could not be determined. There was no albumin, but three pus cells were observed in each high power field. Blood examination revealed: hemoglobin, 38 per cent. (von Fleischl-Miescher); red blood cells, 3,680,000; white blood cells, 10,000. Differential count revealed: polymorphonuclears, 42 per cent.; lymphocytes, 45 per cent.; transitionals, 3 per cent.; eosinophils, 9 per cent.; basophils, 1 per cent. Morphologic examination: There was marked anisocytosis; poikylocytosis and polychromatophilia. The red blood cells contained a very small amount of hemoglobin. The blood was found to be in Group IV repeatedly. The blood Wassermann reaction was negative repeatedly. The Pirquet and Manteau reactions were negative.

TABLE 1.—Comparative Data Regarding Hemoglobin and Red Blood Cell Counts (Case 1)

Date	Time After Trans-fusion	Blood Examination		Comment
		Hemoglobin, per Cent.	Erythro-cytes	
8/22	a.m.	38.0	3,680,000	Smears show severe secondary anemia
8/25	a.m.	39.0	4,300,000	
9/ 1	a.m.	38.0	4,000,000	Transfused 50 c.c. of citrated blood intraperitoneally
9/ 2	a.m.	45.0	4,320,000	
9/ 3	a.m.	47.0	4,500,000	
9/ 5	a.m.	45.0	4,600,000	
9/ 8	a.m.	45.0	4,500,000	Transfused 100 c.c. of citrated blood intraperitoneally
	1 hr.	52.5	5,300,000	
	2 hrs.	55.0	6,000,000	
	3 hrs.	52.5	5,800,000	
	4 hrs.	52.5	5.820,000	
	5 hrs.	49.0	4,730,000	Occult blood in urine
9/ 9	a.m.	55.0	5,900,000	
9/10	a.m.	66.5	5,740,000	
9/11	a.m.	59.5	5,200,000	
9/12	a.m.	57.0	5,000,000	
9/13	......	59.5	5,170,000	Transfused 100 c.c. of citrated blood (50 c.c. intravenously, 50 c c. intraperitoneally)
		61.0	6,130,000	Immediately following transfusion
	1 hr.	63.0	6,060,000	
	2 hrs.	63.0	5,620,000	
	3 hrs.	63.0	5,620,000	
	4 hrs.	63.0	5,040,000	
	5 hrs.	63.0	5,020,000	Occult blood in urine
9/14	a.m.	63.0	5,360,000	
9/15	a.m.	66.5	5,860.000	
9/16	a.m.	63.0	5,630,000	
9/17	a.m.	73.5	6.300,000	Immediately following a bath
9/18	a.m.	68.6	5,780,000	
9/19	a.m.	65.2	5,380,000	
9/23	a.m.	66.5	5,400,000	
9/26	a.m.	70.0	5,680,000	
10/ 2	a.m.	68.6	5,960,000	
10/10	a.m.	70.0	5,730,000	
10/18	a.m.	71.0	5,900,000	

Subsequent Findings.—Aug. 25, 1922, a definite pallor was evident, the result of a marked secondary anemia. Blood examination revealed: hemoglobin, 39 per cent.; erythrocytes, 4,300,000; leukocytes, 8,200; many irritation types of transitional and mononuclear blood cells. Platelets were numerous. There were good bone marrow reactions. The feces were negative when examined for ova or parasites.

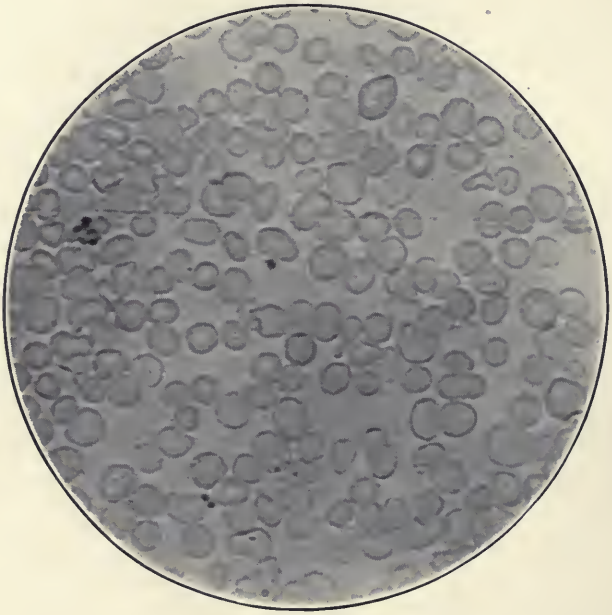


Fig. 2 (Case 1).—Blood picture before transfusion, Sept. 1, 1922, showing evidence of secondary anemia, with marked loss of hemoglobin in the cells. The drawings reproduced here were made with the aid of the camera lucida. The unit of magnification is about 1,500 diameters for all the illustrations. The photomicrographs were made with a Zeiss photomicrograph outfit, the unit of magnification being 570 diameters. In making the photomicrographs, we adhered to a uniform technic. They were taken by Mr. H. W. Morris. The drawings were made by Miss Jean E. Hirsch and Dr. George H. Childs. The charts were prepared by Mrs. R. E. Scammon.

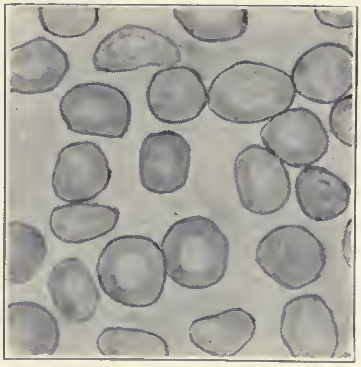


Fig. 3 (Case 1).—Higher power magnification of specimen shown in Figure 2.

September 1, the patient was given 50 c.c. of citrated blood intraperitoneally. Some rise of temperature and pulse reaction followed (Fig. 1). The child lay very quiet and was listless. There were no symptoms of distress.

September 4, the blood picture showed a slight improvement. The appetite was returning. The patient sat up occasionally.

September 10, 100 c.c. of citrated blood was injected intraperitoneally. The febrile and pulse reactions were more moderate than after the first transfusion. There was no evidence of abdominal distress.

September 13, the patient was taken to the surgical ward. The vein in the bend of the elbow was exposed, and 50 c.c. of citrated blood was injected. Difficulties then encountered made it necessary to give the remaining 50 c.c. intraperitoneally. There was a moderate reaction.

September 17, the boy was doing well, and appeared to be happier and brighter since the condition of the blood had improved; in fact, he could not have done better clinically, so far as the blood condition was concerned, if blood had been given intravenously (Dr. H. S. Lippman).

October 31, the boy returned to the dispensary. He was a normal, contented child. Physical examination was entirely negative. The blood picture showed: hemoglobin, 70 per cent.; red blood cells, 5,900,000.

Comment.—It can be seen that the procedure is apparently harmless. The transfusions were accompanied by a temporary rise in temperature and pulse rate during the absorptive period. The reactions became less severe with each subsequent transfusion. There was no evidence of abdominal distress at any time.

In Figure 1, there is a definite rise in the hemoglobin percentage and in the red blood cell counts immediately following each transfusion, with a subsequent rapid fall during the fifth hour. Occult blood was found in the urine coincident with the fall in the blood picture. There is always a more permanent increase in blood values the following day.

A study of our blood smears reveals a gradually increasing number of deeply staining, morphologically normal, red blood cells following each transfusion. They are in distinct contrast to the pale, irregular cells of the patient. No nucleated corpuscles could be demonstrated at any time.

CASE 2.—*Congenital syphilis. History.*—A boy, aged 3 months, American, was brought to the service of Dr. E. J. Huenekens, in the Minneapolis General Hospital, Aug. 28, 1922. He had a discharge from the nose and ears, and snuffles. His mother had syphilis. He was a full-term baby, born in a normal delivery, and was the first child. He had been breast fed since birth, but had never been well. He started to snuffle at 2 months, and vomited after nursing. The weight on entrance was 3,650 gm.

Physical Examination.—The patient was poorly nourished, dehydrated and looked very ill. His temperature was 99 F. The anterior fontanel was wide open, but was not bulging. The sagittal suture and the posterior fontanel were also open. The head circumference was 37 cm. The eyes were negative. There was a purulent discharge from the right ear, and a bloody, purulent discharge from the nose. There was no adenopathy. The heart and lungs were negative. There was an umbilical hernia; the liver was palpable 1 cm. below the costal margin; the spleen was palpable 3 cm. below the costal margin. There was also a bilateral hydrocele. The palms and soles were shiny, with slight exfoliation.

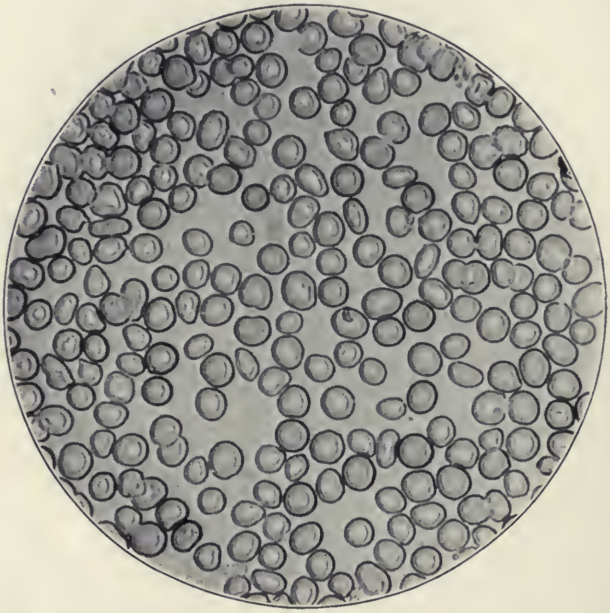


Fig. 4 (Case 1).—Blood picture following transfusions, Sept. 15, 1922, showing numerous deeply stained red blood cells, with uniform morphologic structure.

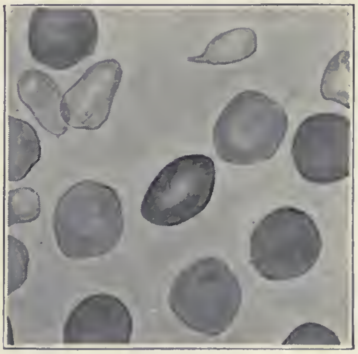


Fig. 5 (Case 1).—Higher power magnification of specimen shown in Figure 4.

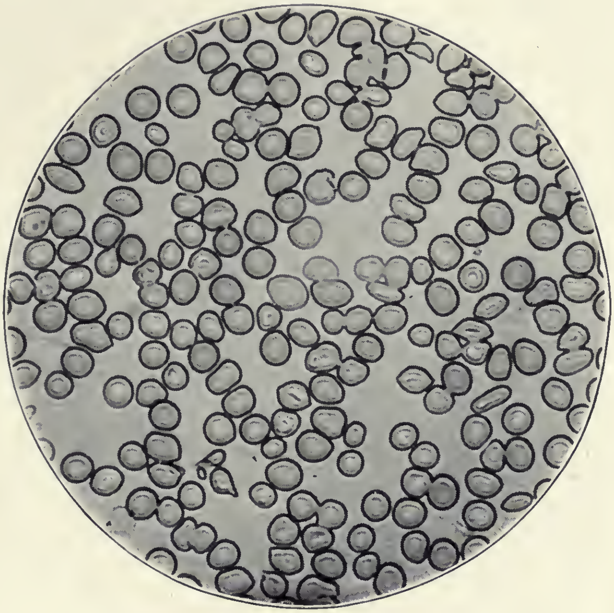


Fig. 6 (Case 1).—Blood picture after one month (Oct. 18, 1922). The recipient's cells may be compared with the donor's (?). Compare with Figures 2, 3, 4 and 5.

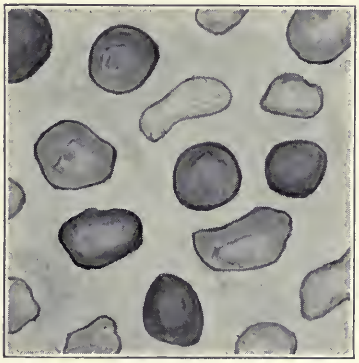


Fig. 7 (Case 1).—Higher power magnification of specimen shown in Figure 6.

Laboratory Findings on Admission.—The urine was amber, and was neutral in reaction; and the specific gravity could not be determined. It contained a faint trace of albumin, and 2 pus cells in each high power field. Examination of the blood revealed: hemoglobin, 56 per cent. (von Fleischl-Miescher); red blood cells, 3,260,000; white blood cells, 10,900. Differential count revealed: polymorphonuclears, 35 per cent.; lymphocytes, 62 per cent.; transitionals, 2 per cent.; eosinophils, 1 per cent. The blood Wassermann reaction was positive with alcohol and cholesterin. The boy's blood belonged to Group II, the mother's blood belonged to Group IV. The Pirquet reaction was negative.

Subsequent Findings.—September 8: Antisyphilitic treatment produced no change in the boy's general condition.

September 15, he was given 50 c.c. of citrated blood intraperitoneally. No temperature or pulse reaction followed.

TABLE 2.—Comparative Data Showing Blood Values and Ashby Counts of Unagglutinated Cells (Case 2)

Date	Time	Blood Examination		Unagglutinated Cells	Comment
		Hemoglobin, per Cent.	Erythrocytes		
8/28	a.m.	56	3,260,000		
9/14	a.m.	59.5	3,800,000	21,450	Control; checked repeatedly
9/15	3 p.m.	59.5	3,980,000	36,850	Transfused 50 c.c. of citrated blood intraperitoneally
	5 p.m.	56	5,160,000	33,550	Group IV
9/16	a.m.	56	5,280,000	106,700	
	p.m.	63	4,410,000	308,000	
9/17	a.m.	66	4,080,000	82,500	
9/19	a.m.	91	5,400,000	....	Sinus transfusion, 150 c.c.; Group II blood
9/23	a.m.	82	5,560 000		

September 17, no improvement was noticeable. All urine specimens were negative for occult blood.

September 19, the boy was given 150 c.c. of citrated blood by the sinus route. There was an immediate rise in the blood picture (Table 2). The urine showed the presence of occult blood.

September 27, the boy had gained 400 gm. in weight in a week. He did not regurgitate his food and nursed well. He was discharged and antisyphilitic treatment was continued in the outpatient department.

Comment.—This patient was admitted in a condition of severe decomposition. . The blood group afforded an opportunity to apply Ashby's method of demonstrating the corpuscles of the donor in the general circulation of the recipient. The physical condition of the patient (slow respiration, sluggish peristalsis) probably delayed a rapid absorption of the injected blood. There was apparently a definite increase in the number of unagglutinated (Group IV?) cells. Because of conditions already mentioned, we cannot draw any definite conclusions from this case.

The clinical course made a sinus transfusion imperative, with the results shown in Table 2.

Case 3.—*Decomposition. History.*—A girl was born in the Minneapolis General Hospital, Sept. 7, 1922, on the service of Dr. E. J. Huenekens. She was underweight, and suffered with diarrhea. Her mother was in the hospital with eclampsia. Otherwise, her history was negative. There was no history

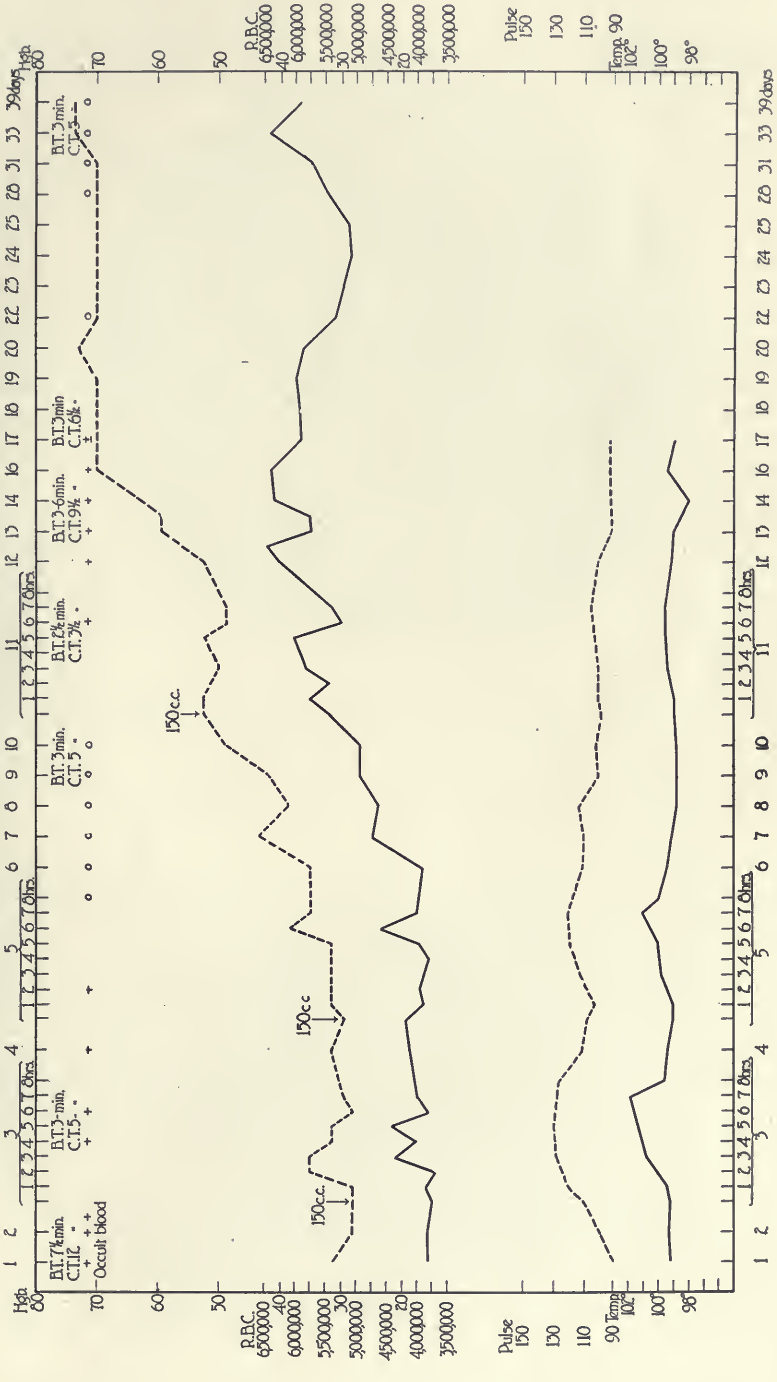


Fig. 8.—Graphic presentation of Table 3 (Case 4), showing temperature and pulse reactions.

of venereal disease. The child, the sixth in the family, was born prematurely by one month, with a normal delivery. The weight at birth was 2,350 gm. She had been tube fed with breast milk since birth. When she was transferred to the pediatric service on the seventeenth day, the weight was 2,350 gm. She was placed on breast milk, which was complemented up to 3 ounces with casein milk plus 5 per cent. dextrimaltose.

Physical Examination.—The child was an emaciated, markedly dehydrated infant, with fair development, but poor nutrition. The body temperature was 99 F. The anterior fontanel was open, but not bulging. The eyes, ears, nose and throat were negative; likewise the heart and lungs. No marked adenopathy was evident. The abdomen was markedly distended. The spleen was palpable. The extremities were negative.

Laboratory Findings on Admission.—The urine was acid, and contained no albumin or casts; the specific gravity could not be determined. Clumps of leukocytes were present. Blood examination revealed: hemoglobin, 90 per cent. (Tallqvist); erythrocytes, 4,230,000; leukocytes, 9,200. Differential count was: polymorphonuclears, 64 per cent.; lymphocytes, 36 per cent. The blood belonged to Group IV. The blood Wassermann reaction and the Pirquet reaction were negative.

Subsequent Findings.—September 26, the child was given 280 c.c. of physiologic sodium chlorid solution intraperitoneally.

September 29, it was given 380 c.c. of physiologic sodium chlorid solution.

September 30, the baby regurgitated its feedings. It now weighed 2,200 gm., and was losing ground rapidly. On becoming moribund, it was injected with 100 c.c. of citrated blood intraperitoneally. The temperature rose to 102.6 F. (rectal), but dropped to normal in twelve hours.

October 1, some improvement was manifest. The child took its feedings, but continued to regurgitate.

October 3, the baby was cyanotic, and was breathing with difficulty. The lungs showed evidence of massive bronchopneumonia. It died one hour after examination.

Necropsy.—The peritoneal cavity contained about 30 c.c. of blood; there were no adhesions or clots. The lungs showed widespread pneumonia. All other organs were negative.

Comment.—This patient was moribund when she received the transfusion. At necropsy, performed three days later, 30 c.c. of thick blood was recovered. Apparently, about 70 c.c. of blood was reabsorbed from the peritoneal cavity even in this extreme condition.

It has been shown by many investigators, von Recklinghausen,[10] Muscatello,[11] Wagner,[12] Zimmermann[13] and others that absorption from the peritoneal cavity is materially aided by the active peristaltic movements of the intestines and by the sucking action of the diaphragm during normal inspiration and expiration. These factors were, of course, markedly impaired in this case.

---

10. Von Recklinghausen, F. V.: Zur Fettresorption, Virchows Arch. f. path. Anat. **26**:172-208, 1863.

11. Muscatello, G.: Ueber den Bau und das Aufsaugungsvermögen des Peritonäums, Virchows Arch. f. path. Anat. **142**:327-360 (Nov.) 1895.

12. Wagner, Arthur: Zur Behandlung der geplatzten Extra-uteringravidität mit freier Blutung, Deutsch. med. Wchnschr. **38**:1457-1460 (Aug.) 1912.

13. Zimmermann, Robert: Ueber die Indikationstellung zur Retransfusion in die Bauchhöhle ergossenen Blutes, Ztschr. f. Gebürtsh. u. Gynäk. **84**:334-355 (Nov.) 1921.

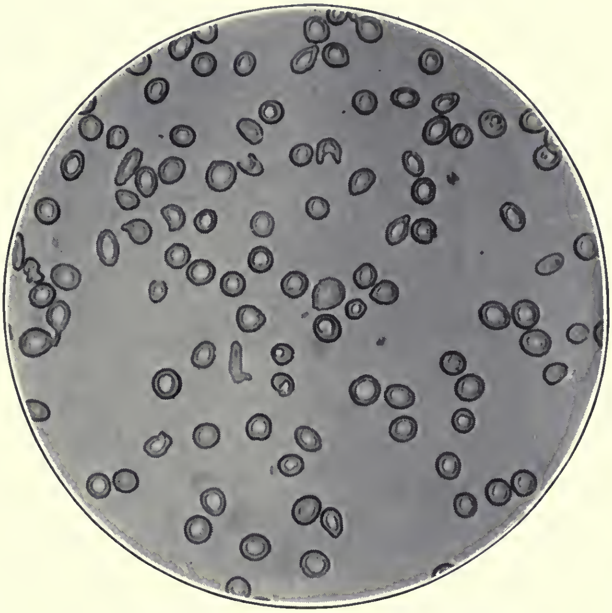


Fig. 9 (Case 4).—Blood picture before transfusion, Sept. 27, 1922, showing evidence of secondary anemia and numerous microcytes.

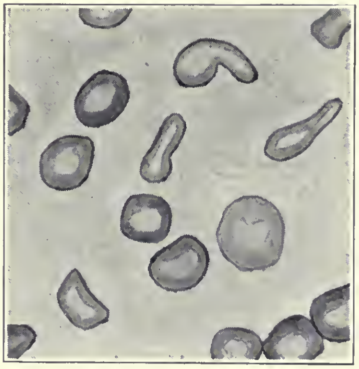


Fig. 10 (Case 4).—Higher power magnification of specimen shown in Figure 9.

Case 4.—*Hemolytic anemia; hemoglobinuria. History.*—A girl, aged 16 months, American, was brought to the service of Dr. E. J. Huenekens at the Minneapolis General Hospital, Sept. 25, 1922, because of extreme pallor, poor appetite and weakness since birth. The history was negative, and there was no history of venereal disease. The baby, the first child, was born at full term, with a normal delivery. She was breast fed for eleven months; then was given whole cow's milk, and cereals and vegetables were added to the diet. She developed normally. The first tooth appeared at 6½ months; but the baby did not walk at the time of admission. She had had no diseases except diarrhea at 12 months, which persisted for several weeks. The history by systems was negative.

Physical Examination.—The patient was in bed, and showed marked pallor. The development was good, and nutrition, fair. The baby was apathetic and irritable. The temperature was 100 F.; pulse, 120. The head was square. The anterior fontanel was nearly closed. The eyes, ears, nose and throat were negative. There was no marked adenopathy. The lungs were also negative. A systolic murmur was audible over the precordium and was transmitted to the back. The pulmonic second sound was present. Inspection of the abdomen suggested "pot-belly." The liver was palpable. The spleen was negative. The extremities were also negative, as was the neuromuscular system. The weight on entrance was 16 pounds (7,263 gm.).

Laboratory Findings on Admission.—The urine was acid in reaction. It contained a faint trace of albumin and two leukocytes in each high power field, but no casts, no urobilin or urobilinogen. The specific gravity was not determinable. The benzidin reaction was markedly positive. Examination of the stool was negative repeatedly for blood. Blood examination revealed: hemoglobin, 31.5 per cent. (von Fleischl-Miescher); red blood cells, 3,810,000; white blood cells, 16,000; differential count: polymorphonuclears, 49 per cent.; lymphocytes, 46 per cent.; transitionals, 3 per cent.; eosinophils, 1 per cent.; basophils, 1 per cent. The blood Wassermann reaction was negative repeatedly. The bleeding time was seven and one-half minutes; the clotting time was twelve minutes. The blood belonged to Group IV. There were 450,000 platelets for each cubic millimeter.

Fragility Test: There was beginning hemolysis, 0.46 per cent.; complete hemolysis, 0.34 per cent.

Morphologic Examination: The majority of cells were much smaller than normal. There were many poikilocytes; numerous macrocytes, and polychromatophils. The cells were pale and appeared to be almost without hemoglobin in the center. There were no nucleated red blood cells, and there was no evidence of blood regeneration. The Wassermann reactions of the parents were negative. The roentgen-ray examination of the head and long bones was negative.

Subsequent Findings.—September 27, an intraperitoneal transfusion of 50 c.c. of citrated blood was made. A moderate febrile reaction resulted (Fig. 8). There were no subjective symptoms. The patient gave no evidence of distress.

September 29, an intraperitoneal injection of 150 c.c. of citrated blood was made. The following febrile and pulse reaction was less than that following the first transfusion (Fig. 8). The patient had a good day. There was no evidence of distress, and there were no subjective symptoms.

October 3, the appetite was improving. The baby was more active, sat up in bed and was becoming more playful. The blood picture was improving. The bleeding time was less than three minutes; the clotting time was less than five minutes.

October 22, there was marked clinical improvement. The bleeding time was three minutes; the clotting time, six and one-half minutes. The benzidin and guaiac reactions of the urine were still positive. The cause of the hemoglobinuria (?) was obscure. The baby weighed 17.5 pounds (7,988 gm.).

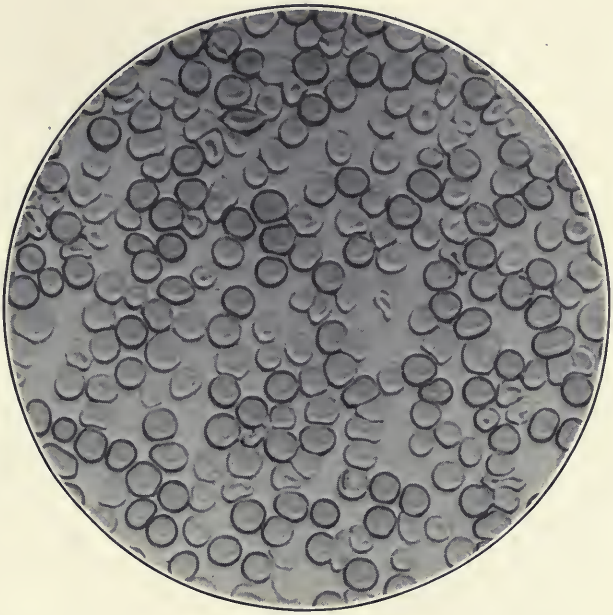


Fig. 11 (Case 4).—Blood picture following transfusions, Oct. 10, 1922. The patient's cells may be contrasted with large, uniform, deeply stained erythrocytes (donor's cells ?).

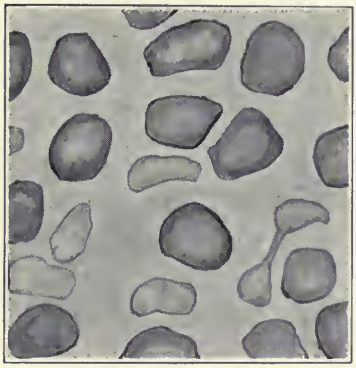


Fig. 12 (Case 4).—Higher power magnification of specimen shown in Figure 11.

TABLE 3.—Comparative Data Regarding Hemoglobin and Erythrocyte Counts (Case 4)

Date	Time	Blood Examination		Occult Blood in Urine: +, Present; 0, Absent	Bleeding Time, Min.	Clotting Time, Min.	Comment
		Hemoglobin, per Cent.	Erythrocytes				
9/25	a.m.	31.5	3,800,000	+ (benzidin)	7½	12	
9/26	a.m.	28.0	3,700,000	+ (benzidin)			
9/27	9 a.m.	28.0	3,760,000	....	..	..	Intraperitoneal transfusion with 50 c.c. of citrated blood at 10 a.m.
	11 a.m.	28.0	3,870,000				
	12 m.	35.0	3,670 000				
	1 p.m.	35.0	4,340,000	....	3	5	
	2 p.m.	31.5	4,000,000				
	3 p.m.	31.5	4,400,000				
	4 p.m.	28.0	3,800 000				
	5 p.m.	29.4	3,990,000	+ (benzidin)			
9/28	a.m.	31.5	4,100,000				
	p.m.	28.0	3,400,000				
9/29	9 a.m.	29.4	4,170,000	....	..	..	Intraperitoneal transfusion with 50 c.c. of citrated blood at 10 a.m.
	11 a.m.	31.5	3,890,000				
	12 m.	31.5	3,930,000				
	1 p.m.	31.5	3,800,000				
	3 p.m.	31.5	3,960,000				
	4 p.m.	38.5	4,590,000				
	5 p.m.	35.0	4,000,000				
9/30	a.m.	35.0	3,900,000	0 (benzidin)			
10/ 1	a.m.	43.4	4,720,000	0 (benzidin)			
10/ 2	a.m.	38.5	4,630,000	0 (benzidin)			
10/ 3	a.m.	42.0	4,920,000	....	3	5	
10/ 4	a.m.	49.0	4,930,000	0 (benzidin)			
10/ 5	9 a.m.	52.5	5,440,000	+ (benzidin)	..	..	Intraperitoneal transfusion with 150 c.c. of citrated blood at 10 a.m.
	11 a.m.	52.5	5,740,000				
	12 m.	45.5 ?	5,440,000				
	1 p.m.	50.0	5,800,000				
	3 p.m.	52.5	6,000,000				
	4 p.m.	49.0	5,230,000	....	2½	3½	
	5 p.m.	49.0	5,400,000	+ (benzidin)			
10/ 6	a.m.	52.5	6,260,000				
	p.m.	56.0	6,450,000	+ (benzidin)			
10/ 7	a.m.	59.0	5,720,000	+ (benzidin)	3-6	9½	
	p.m.	59.0	5,720,000				
10/ 8	......	63.0	6,370,000	+ (benzidin)			
10/10	a.m.	70	6,380,000	+ (benzidin)			
10/11	a.m.	72	5,900,000				
10/12	a.m.	72	5,910,000	+ (benzidin)	3	6½	
10/13	a.m.	70	5,970,000				
10/14	a.m.	73	5.840,000	+ (benzidin), 0 (guaiac)			
10/16	a.m.	70	5,310,000	+ (benzidin), 0 (guaiac)			
10/17	a.m.	70	5,200,000	0 (benzidin and guaiac)			
10/18	a.m.	70	5,090,000	+ (benzidin), Tr. guaiac			
10/19	a.m.	70	5,110,000				
10/20	a.m.	70	....	+ (benzidin and guaiac)			
10/22	a.m.	70	5,490,000	0 (benzidin and guaiac)			
10/25	a.m.	70	5,700,000	0 (benzidin and guaiac)			
10/27	a.m.	73.5	6,400,000	0 (benzidin and guaiac)	3	5	
11/ 2	a.m.	73.5	5,980,000	0 (benzidin and guaiac)			

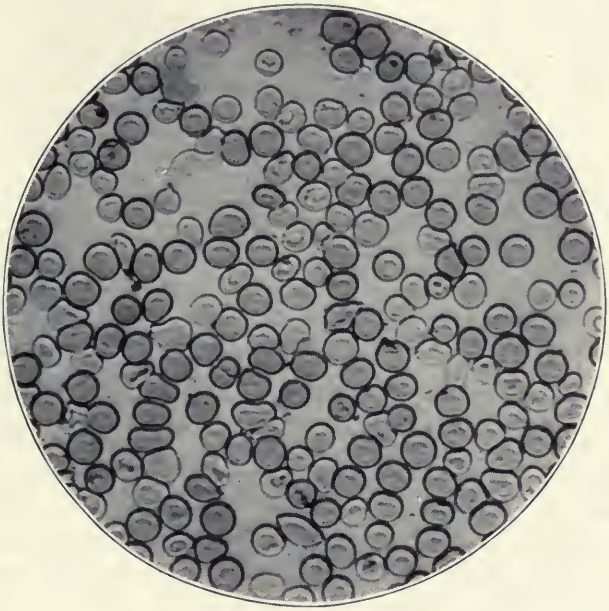


Fig. 13 (Case 4).—Blood picture after discharge from the hospital, Oct. 25, 1922. Compare with Figures 9, 10, 11 and 12.

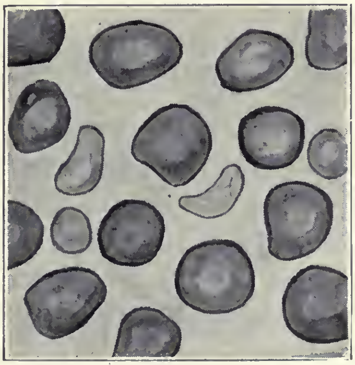


Fig. 14 (Case 4).—Higher power magnification of specimen shown in Figure 13.

October 28, there had been no evidence of occult blood in the urine during the preceding week. The clinical condition of the patient was good. He stood up with slight assistance. He was discharged to the outpatient department.

Comment.—This case is somewhat complicated because of the apparent destruction of erythrocytes within the patient's body. The etiology of the positive benzidin and guaiac reactions in the urine has, up to the present time, not been determined. All urine specimens were amber and clear. There was never any evidence of hematuria, only that of a hemoglobinuria.

Is this a case of hemolytic anemia and are our results due to a remission in the clinical course of the disease? Only time will answer definitely, but several factors speak against this possibility.

The mother states that the child never showed any periods of improvement from the time of birth, and that its condition on discharge was much better than it had ever been. We should certainly expect a history of previous remissions.

If the blood curves represent a remission, the smears should show evidence of blood regeneration. To compensate for the unquestionable improvement in the blood picture, we ought to find many nucleated erythrocytes in the general circulation. In a careful study of numerous slides we were unable to demonstrate nucleated red blood cells at any time during the patient's stay in the hospital.

Furthermore, a morphologic study of the corpuscles of the patient revealed that the cells were, for the most part, microcytes. There were also numerous macrocytes. The cells appeared to be almost without hemoglobin content.

Following the transfusions, there could be found in the blood stream numerous deeply stained cells, with a normal morphologic structure. I am convinced that these were the erythrocytes of the donor. The contrast between the corpuscles of the patient and those of the donor was very striking. Among the normal red blood cells of the donor, there could always be found the much smaller, pale cells of the recipient.

From the evidence presented, I feel justified in considering that the unquestionable clinical improvement in this case was due to the intraperitoneal transfusions themselves, and not to a coincident remission.

The report of Case 5 was supplied by Dr. E. D. Anderson:

CASE 5.—*Secondary anemia. History.*—A girl, aged 3 weeks, American, was markedly jaundiced, and had been vomiting excessively for one week. Her parents were living and well. Two children were living and well. One child died two weeks after birth. The diagnosis was congenital obliteration of the bile ducts. The patient, the fourth child, was a baby born at full term, in a normal delivery, and had been breast fed since birth. Physical examination at birth was negative. Two weeks after birth, the patient became markedly jaundiced within twenty-four hours, and vomited about every fifteen minutes. There was no bleeding from the mouth or intestines and no elevation of temperature. The child was first seen thirty-six hours after the onset of symptoms.

Physical Examination.—The temperature was normal. The patient showed marked pallor of the skin and mucous membranes, with a slight icteric tinge of the skin. Examination otherwise was entirely negative.

Laboratory Findings.—The urine and stool were negative. Blood examination revealed: hemoglobin, 20 per cent.; red blood cells, 1,472,000; white blood cells, 2,800; differential count: polymorphonuclears, 63 per cent.; lymphocytes, 16.5 per cent.; large mononuclears, 1.5 per cent.; transitionals, 3 per cent.; eosinophils, 5 per cent.; basophils, 1 per cent.; myelocytes, 10 per cent. In a count of 200 cells, sixty-four nucleated red blood cells were seen. There was slight anisocytosis. The erythrocytes were small and contained little hemoglobin. The bleeding time was two minutes and thirty seconds. The clotting time was four minutes. The fragility test was normal.

Subsequent Findings.—The first day, the patient was given 40 c.c. of whole blood, subcutaneously.

The second day, she was given 40 c.c. of whole blood. There was no rise in the hemoglobin percentage.

The fourth day, 30 c.c. of citrated blood was given through the sinus route. The hemoglobin was 36 per cent.

The seventh day, the hemoglobin was 23 per cent.

The tenth day, 100 c.c. of citrated blood was given through the sinus route. The hemoglobin was 34 per cent.

The twentieth day, the hemoglobin was 31 per cent. The patient had been given pills of ferrous carbonate (Blaud's), in 3 grain (0.195 gm.) doses by mouth, three times daily, for the preceding ten days. One hundred cubic centimeters of citrated blood was injected by the sinus route. The hemoglobin was 49 per cent. The physical examination was negative. There was no evidence of hemorrhage. The baby nursed well and was gaining normally.

The twenty-seventh day, the spleen was palpable, 4 cm. below the costal margin. The hemoglobin was 52 per cent.

The thirty-fourth day, the hemoglobin was 35 per cent. A vein in the elbow was exposed by the surgeon; but transfusion by this means was rendered impossible through technical difficulties. (The surgical incision did not heal for a month, owing to the patient's physical condition.)

The forty-first day, the baby was given 90 c.c. of citrated blood by the sinus route.

The forty-fourth day, the hemoglobin was 39 per cent.

The fifty-fourth day, the hemoglobin was 31 per cent. The baby was given 70 c.c. of citrated blood intraperitoneally. The temperature rose to 103 F. There was considerable distention and discomfort. Twenty-four hours later, the temperature was normal, and the patient appeared to be perfectly comfortable.

The fifty-sixth day, the hemoglobin was 26 per cent.

The sixty-third day, the baby was given 100 c.c. of citrated blood intraperitoneally. The hemoglobin was 39 per cent.

The sixty-eighth day, the baby was given 100 c.c. of citrated blood intraperitoneally. The hemoglobin was 50 per cent.

The seventy-eighth day, the baby was given 70 c.c. of citrated blood intraperitoneally. The hemoglobin was 59 per cent.

The ninetieth day, physical examination revealed that the child was in excellent general condition. The spleen was still slightly palpable.

Comment.—The first intraperitoneal injection of citrated blood was followed by a reaction. The subsequent transfusions were well borne. There was no rise in temperature and the patient showed no evidence of discomfort. The sinus route was used repeatedly, until it became accessible only with difficulty. Surgical assistance failed. The intraperitoneal transfusion produced a definite rise in the hemoglobin estimations and a definite improvement in the infant's clinical condition.

There is danger of peritonitis following the puncture of the intestine. However, the clinical experience of numerous observers has demonstrated that this possibility is remote. At the present time, it does not deter pediatricians from using the intraperitoneal route for the injection of physiologic sodium chlorid solution or glucose in athreptic infants. "If a short bevel needle is used and reasonable care taken, it is almost impossible to do any damage to the intestine, a fact attested by many observers" (Porter and Carter [14]). It is employed almost as a routine measure in many hospitals, and, in many instances, it is used in preference to the subcutaneous method.

This wide popularity can only mean that the dangers inherent in this procedure are very slight, and that peritonitis following abdominal puncture is not a common incident.

There is always a definite pulse and temperature reaction following the first transfusion. This reaction becomes less severe with each subsequent transfusion. There were no toxic symptoms or evidence of abdominal distress.

Recently, Halbertsma [15] suggested a formula for calculating the rise in the erythrocyte count following the injection of blood. It was thought that comparative results, while of no definite value, would be interesting (Table 4).

TABLE 4.—Comparison of Theoretical with Actual Rise in the Number of Red Blood Cells Following Transfusion

Case	Transfusion	Number of Red Blood Cells	
		Actual Rise	Theoretical Rise
1	First	300,000	330,000
1	Second	1,500,000	660,000
1	Third	900,000	660,000
4	First	500,000	500,000
4	Second	500,000	1,400,000
4	Third	500,000	1,400,000

I believe that the intraperitoneal transfusion of citrated blood is a therapeutic method that should be utilized clinically in selected cases. With the gradual accumulation of more clinical data, we hope that, in time, we shall have a definite list of indications. It would already appear that the proposed route cannot be used in an emergency. In any emergency case, a direct transfusion into the circulation is demanded.

---

14. Porter, Langley, and Carter, W. E.: Management of the Sick Infant, St. Louis, C. V. Mosby Company, 1922, p. 20.

15. Halbertsma, Tj.: The Amount of Blood to Be Transfused in Anemia of Children (Blood Dosage), Am. J. Dis. Child. **24**:269 (Oct.) 1922.

SUMMARY

No benefit accrued from medical treatment for the anemia in Case 1. A transfusion was definitely indicated. The anterior fontanel was closed, and exposure of a vein was difficult. Nevertheless, this was attempted, with only partial success. Intraperitoneal transfusions gave immediate, favorable results.

In Case 2, an irresistable opportunity was afforded to apply the method devised by Ashby. The patient's condition necessitated a sinus transfusion before the outcome of the previous operation could be determined.

The patient in Case 3 was a dehydrated, emaciated, moribund infant, 17 days old. One hundred c.c. citrated blood was given intraperitoneally. About 30 c.c. was recovered at the postmortem, three days later. Absorption undoubtedly was delayed because of the extremely serious condition of the patient.

Case 4 presented a picture of blood destruction. Transfusion was clearly indicated. The anterior fontanel was almost closed. The intraperitoneal method was the only practical procedure. A noticeable clinical improvement followed the transfusions.

No benefit accrued from medical treatment in Case 5. Subcutaneous injections of whole blood failed to help. Sinus transfusion, as long as the sinus was accessible, was resorted to with some success. Surgical intervention failed. Intraperitoneal transfusions have apparently resulted in a marked improvement in the patient's clinical condition.

Among the five cases reported, favorable results were obtained in three. The intraperitoneal transfusion of citrated blood is simple to apply, practical and efficient. The intra-abdominal route should, if possible, not be the method of choice in emergency cases. When the anterior fontanel is closed and surgical exposure of a vein is difficult, this new avenue of approach is suggested.

CONCLUSIONS

1. The intraperitoneal transfusion of citrated blood is a therapeutic procedure of possible merit.

2. It can apparently be utilized in cases in which transfusion is indicated, when other routes are unavailable or impractical.

POLYCYSTIC DISEASE OF THE KIDNEYS

REPORT OF CASE IN AN INFANT *

ABRAHAM TOW, M.D.
House Pediatrician, Lenox Hill Hospital
NEW YORK

The occurrence of polycystic disease of the kidneys in infancy is uncommon. Of the case reports in the literature, in only one[1] are the phenolsulphonephthalein excretion and a partial chemical determination of the blood mentioned. The case herewith reported is, therefore, of special interest because it contains the results of phenolsulphonephthalein determinations and a complete chemical study of the nitrogenous constituents of the blood, together with the other findings.

REPORT OF CASE

History.—L. B., boy, aged 6 weeks, was admitted to the Abraham Jacobi Division for Children, Lenox Hill Hospital, Sept. 18, 1922. The mother had had severe headaches and abdominal pains for two days before delivery, but the birth and puerperium had been normal. The baby weighed 7 pounds (3,175 gm.). Symmetrical swellings in both lumbar regions were noticed at birth. The child cried a great deal; but it had had no illnesses to the mother's knowledge.

The child was breast fed. The stools were normal. There was no history of urinary disturbances. He vomited once on the day before admission, though it was not evident that this bore any relation to feeding.

The mother was 24 and the father 30 years old. The father had been married previously; but his first wife was never pregnant. The second marriage had been of one year's duration, and this was the first child. There was no history of malignancy or tumor formation in either family.

Examination.—The weight was 7 pounds 4 ounces (3,289 gm.). The height was 20½ inches (51.2 cm.). The patient was white and well developed but poorly nourished. He was cyanotic, and scattered over the body was a papular rash, most marked over the extremities. The skin was loose, flaccid, and dry, and it was covered with large flaky scales. The axillary and inguinal glands were palpable on both sides. The muscle tone was poor.

The circumference of the head was 14½ inches (36 cm.); both fontanels and the cranial sutures were open. No masses were felt, nor points of tenderness elicited. The pupils were equal and reacted to light and accommodation. Blepharitis was present in both eyes, more marked in the right. Examination of the eyegrounds was negative. The ears, nose, mouth and neck were all negative.

The circumference of the chest was 12½ inches (31 cm.). The lungs were normal. The heart on percussion was slightly enlarged, extending about one-half inch (1.7 cm.) to the left of the left nipple.

---

* Received for publication Feb. 7, 1923.

* From the Abraham Jacobi Division for Children, Lenox Hill Hospital, Dr. A. L. Goodman, Director.

[1] Greene, C. H.: Bilateral Hypoplastic Cystic Kidneys: Report of a Case Simulating Chronic Diffuse Nephritis in a Girl, Three Years of Age, Am. J. Dis. Child. **24**:1 (July) 1922.

The circumference of the abdomen was 15 inches (37.5 cm.) at the umbilicus. The abdomen was distended, and two definite masses were palpable, one in each lumbar region. The mass on the left side was larger than that on the right, though both felt hard and nodular. They extended from the costal margin to the crest of the ilium, and, on the left side, down into the pelvis. Anteriorly, they extended well over toward the midline, and, posteriorly, they were easily palpated and extended almost to the vertebral column.

The abdomen was tympanitic over the ensiform, and the stomach and colon appeared to be pushed forward by the two masses. The liver and spleen were both palpable, but were not enlarged. In addition, there was a diastasis of the recti and a small umbilical hernia. A double hydrocele was also found. The spine and reflexes were normal.

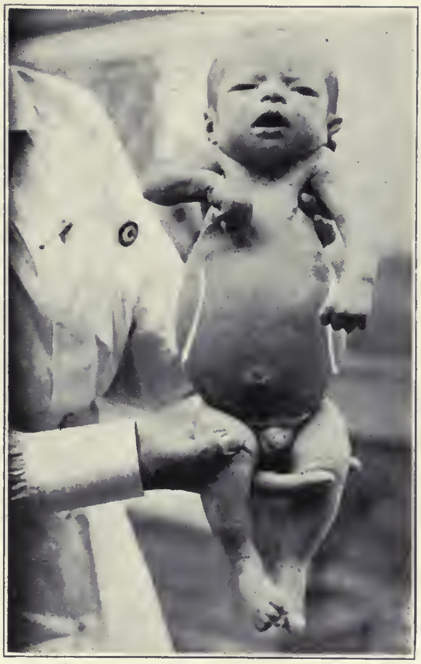


Fig. 1.—Appearance of patient on admission, with the kidneys outlined.

A culture and smear from the eyes revealed *Staphylococcus aureus* and a nonhemolytic streptococcus. Both blood and spinal fluid Wassermann reactions were negative. The Pirquet skin reaction for tuberculosis and the Schick test for diphtheria were both negative. Repeated blood counts, on admission and at several intervals during the course of the disease, revealed from 70 to 55 per cent. hemoglobin. The erythrocyte count was five million on admission and four million before death. The leukocyte count was between 6,000 and 8,000 cells, with 70 per cent. lymphocytes and 30 per cent. polymorphonuclears.

At the time of admission a reducing substance was found in the urine; but, on subsequent examinations, this was not present. A faint trace of albumin was found on the second examination. This persisted. Microscopic examination of the sediment revealed an occasional granular cast and an occasional leukocyte. The specific gravity varied between 10.09 and 10.10. The urinary output varied between 100 and 150 c.c. (A normal infant with an intake of about 700 c.c. ought to excrete in the neighborhood of 300 c.c.)

The phenolsulphonephthalein excretion showed the first trace of the dye (without catheterization) in thirty minutes; though normally, the child should have shown a trace in a catheterized specimen in from five to ten minutes. The specimen for the first hour showed a trace, and the second specimen, taken at two hours and forty minutes instead of two hours, revealed 5 per cent. excretion. The normal figures are from 40 to 60 per cent. in the first hour, and from 20 to 25 per cent. in the second. When the test was repeated, three weeks later, the total dye excreted in two hours was 8 per cent. It is interesting to note that a trace of the dye was found ninety-three hours after the first injection and eighty-four hours after the second.

In a control estimation made on an infant, aged 11 months, recovering from pneumonia, the first trace appeared in ten minutes. The first hour revealed 54 per cent. excretion; the second hour revealed 7 per cent. excretion and the dye had been completely eliminated after twenty hours. The urine of this control patient was normal.

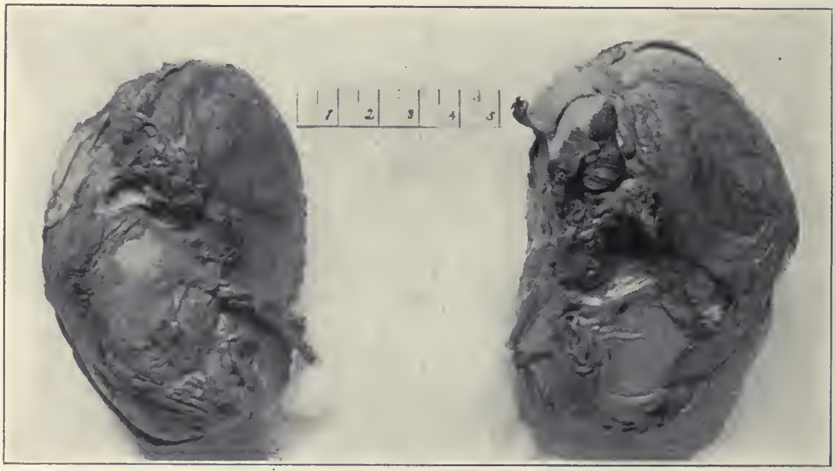


Fig. 2.—Polycystic disease of the kidneys.

A roentgenographic examination made on admission revealed that the heart was enlarged. The transverse diameter was 6.75. An examination made three weeks later demonstrated the transverse diameter to be 7.25 cm.

The results of the chemical examination of the blood are given in the accompanying table.

RESULTS OF CHEMICAL EXAMINATION OF THE BLOOD

	Normal	Sept. 21	Sept. 28	Oct. 11
Urea nitrogen	12-15	38.4	50.0	26.3
Creatin	0.5-2	2.2	1.2	2.36
Uric acid	1-2.5	3.7	4.0	2.8
Sugar, per cent..................	0.8-0.12	0.084	0.086	0.160
Cholesterol	150-200		100.0	188.0
Carbon dioxid combining power:				
Volumes per 100 c.c. blood plasma	53-77		41.0	

The findings when summarized revealed: (1) bilateral abdominal tumors; (2) signs of chronic nephritis: (*a*) albumin and casts in the urine, (*b*) diminished excretion, (*c*) nitrogen retention, and (3) an enlarged heart.

Course.—The patient's stay in the hospital was uneventful until the day before death. The child gained but 12 ounces (341 gm.) in more than five weeks; but it improved greatly in color and muscle tone. On the day before death, it became slightly cyanosed and, on two occasions, dyspneic for a few seconds. Death came suddenly, with signs of pulmonary edema.

Comment.—In the differential diagnosis, syphilis and tuberculosis were eliminated because of the negative blood and spinal fluid Wassermann reactions, the negative Pirquet test and the absence of any clinical evidence of the presence of either.

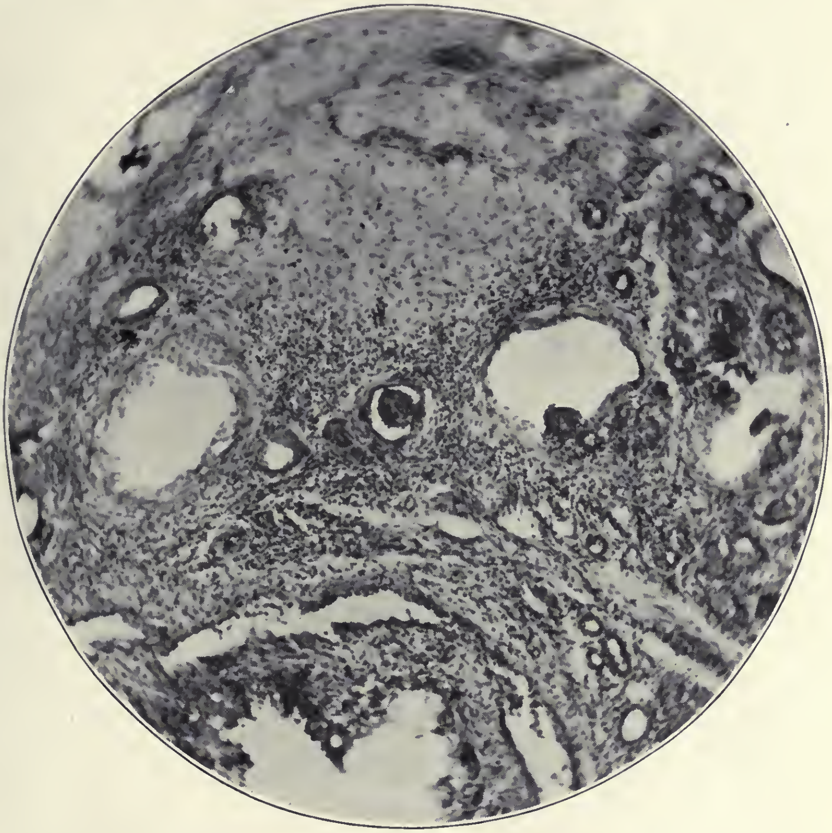


Fig. 3.—Section of the kidney, showing the sparsity of normal kidney tissue (only two glomeruli may be seen in this field), the cysts and the infiltration of the hyaline connective tissue.

The existence of a marked kidney lesion, as shown by the phenolsulphonephthalein test and by the chemical examinations of the blood, confined the possibilities to the kidneys. Hypernephroma, sarcoma and polycystic disease of the kidney were considered.

A congenital, bilateral, almost symmetrical mass dating from birth might be a hypernephroma; but no report of any such condition could be found in the literature. While Jacobi,[2] in a series of fifty-five cases of sarcoma of the kidney, reports five as being congenital. Sarcoma usually does not present two masses of almost equal size. The tendency is for the mass on one side to be much larger than on the other; or, on physical examination, only one tumor mass is palpable.

---

[2] Jacobi, quoted by Holt, L. E.: Diseases of Infancy and Childhood, Ed. 7, New York, D. Appleton & Co., p. 640.

The cases reported here presented the triad of symptoms which made a diagnosis of polycystic disease of the kidneys far from difficult. With the following findings, the diagnosis is almost a certainty: (1) bilateral abdominal tumors dating from birth; (2) signs of chronic nephritis; (3) an enlarged heart.

Pathologic Examination.—The body was that of a somewhat emaciated male infant, 46 cm. in length. It weighed 3,635 gm. The abdomen was protuberant and was almost completely filled with a bilateral tumor mass. Rigor mortis was present. The pupils were dilated.

Skull: When the calvarium was opened, an excessive amount of cerebrospinal fluid escaped. The pia was very markedly edematous, and the convolutions on the inferior portion of the forebrain showed marked flattening. The lateral ventricles were slightly distended.

Chest: Both pleural cavities contained approximately 50 c.c. of a clear fluid. The pericardium contained about 20 c.c. of a clear fluid. The thymus was persistent. Both lungs, in their posterior, inferior portions, were markedly edematous, but without gross evidence of consolidation. The heart weighed 35 gm. and measured 4 by 3 by 4 cm. in diameter. The greatest amount of hypertrophy was noted in the left ventricle.

Abdomen: The peritoneal cavity contained no fluid. The gastro-intestinal tract, suprarenals, bladder, testes, ureters and gallbladder, as well as the pancreas, were normal on gross examination. The liver was of normal size, and, on gross section, showed no abnormalities. The spleen was slightly increased in size, and, on section, it was firm.

The right kidney weighed 190 gm. and measured 9.5 by 5 cm. The left kidney weighed 180 gm. and measured 9 by 5 cm. Both kidneys on section showed innumerable cysts, which varied in size from 0.1 to 0.6 cm. There were also innumerable smaller cysts which could be seen with a hand lens. No margin of kidney tissue was demonstrable.

Anatomic Diagnosis: Edema of the brain; bilateral pleural effusion; edema of the lungs; cardiac hypertrophy; bilateral congenital cystic kidney.

Cause of Death: Edema of the brain; edema of the lungs.

Summary of Microscopic Examination: Of the heart, no changes; of the lungs, a slight edema; of the liver, no changes; of the spleen, a moderate degree of congestion and fibrosis; of the kidneys, a dense hyaline stroma in which there were a few isolated areas of fairly normal kidney epithelium, the larger portion of the specimen consisted of cystlike spaces lined by from one to twelve and fourteen rows of low cuboidal epithelium.

COMMENT

Some years ago Leopold and Künstler[3] reported a case from this service in which the combined weight of the kidneys was 470 gm. The tumors were palpable; the heart was enlarged. This child was 3 months old and weighed 10 pounds (4,536 gm.). Polycystic disease of the kidney was considered as the most likely diagnosis, and this was confirmed by a laparotomy. The case reported by Greene[1] is exceptional in that both kidneys were atrophic, and their combined weight was but 17 gm. These kidneys were not palpable. The heart was not enlarged. The phenolsulphonephthalein test, performed several times, revealed an excretion varying from 4 to 10 per cent. The nonprotein nitrogen was 48 mg. for each hundred cubic centimeters, and the carbon dioxid capacity was 18 per cent. by volume at the same time, although this rose later to 41 per cent. following a transfusion.

---

[3] Leopold, J. S., and Künstler, M. B.: Polycystic Disease of the Kidney in an Infant Three Months Old, Am. J. Dis. Child. **10**:367 (Nov.) 1915.

A brief review of the subject is of interest, although, for a more elaborate discussion, the reader is referred to the articles by Dunger,[4] Reque [5] and Moschowitz.[6] Greene's report, previously mentioned, is also of interest because of the small size of the kidneys.

The disease seems to have a hereditary basis, thus Dunger [4] cites Virchow's case of four children of the same mother in all of whom polycystic kidneys were found. He also mentions five children of another mother; a father, son and nephew, and a father, son and sister with symptoms in other children of the same family.

The polycystic kidney is probably always congenital and with it other congenital defects are found, namely, harelip, cleft palate, cardiac defects, meningocele, spina bifida, anomalies of excess or absence of extremities, hypospadias and atresia and absence of the bladder. In addition to these, Moschowitz, in summing up the findings of Lejars, Luzatto and Johnson, found liver cysts in about 19 per cent. of the cases.

Several theories have been advanced as to the etiology. Virchow [7] first believed the condition due to an intra-uterine obstruction of the kidney tubules by uric acid and lime infarcts. Later, he concluded that the condition was due to an intra-uterine papillitis produced by the irritation of uric acid and lime infarcts. The papillitis produced the characteristic change in Bowman's capsule by causing atresia and obliteration of the collecting tubules. Brigidi and Severi,[7] in 1870, made the assertion that the condition was a multilocular adenocystoma. Their examination revealed an increase in the number of layers of many of the tubules; proliferation of the epithelium in continuity so that the epithelium appeared contorted within the lumen; epithelial sprouts into surrounding connective tissue from the walls of the tubules, and a pseudopapilliferous formation on the inner walls of many of the cysts.

If this were true, one would expect that the epithelial elements in such kidneys would be increased. But Busse and Dunger [7] have shown that such elements are greatly diminished. The place of the epithelial elements is taken by connective tissue. Busse[7] also found that all embryonal kidneys showed the epithelial changes upon which Brigidi and Severi and their followers based their assertions. The importance of the round-cell foci upon which Virchow and Stieda[7] lay such stress as criteria of inflammation has also been minimized by Busse, who found that such foci existed normally in the connective tissue of all fetal kidneys. Many cases of cystic kidney have also been reported in which papillitis could not be demonstrated. Virchow's explanation also fails to explain the associated anomalies.

---

[4] Dunger, R.: Zur Lehre von der Cystenniere mit besonderer Beruchsichtigung ihre Heredität, Beitr. z. path. Anat. u. z. allg. Path. **35**:445, 1904.

[5] Reque, H. A.: Cystic Kidney and Liver, Med. News, New York **87**:210 (July 29) 1905.

[6] Moschowitz, E.: Nonparasitic Cysts (Congenital) of the Liver, with a Study of Aberrant Bile Ducts, Am. J. M. Sc. **131**:674 (April) 1906.

[7] Quoted by Moschowitz, Footnote 6.

The theory of maldevelopment, first suggested by Von Mutach,[7] is the popular one today. This author, in a study of embryonal and cystic kidneys, recognized the striking embryonal characteristics of the cystic kidney. However, it is probable that no one theory is applicable in all cases.

In infancy no child lives long if the tumor masses are palpable. But enough kidney tissue may be left to permit the organs to function sufficiently well so that the patient may live for many years, dying then either of some condition independent of the kidney lesion or because of inability properly to carry on the process of elimination. Of the necropsies performed at this hospital, one was on a woman, 64 years old and very obese, who died of pneumonia following an operation for carcinoma of the breast. Examination of the urine was negative, and no pathologic condition of the kidney was suspected. At necropsy two polycystic kidneys were found. This woman had a cleft palate.

Medical treatment is purely symptomatic. When the cysts become so large that they produce pressure symptoms, multiple puncture of the cysts may afford some relief. In adults, Rovsing[8] and Lund[9] have reported some favorable results following the procedure as adopted by Rovsing. But in the hands of other surgeons, the results have been unfavorable. It is asserted that this operation cannot restore damaged kidney tissue, and sections of such a kidney reveal that only a very small number of the cysts are on the surface. One can readily see, therefore, that puncture of the large cysts may relieve pressure symptoms; but the kidney function can hardly be improved unless, as Rovsing himself says, there is an obstruction due to the pressure. Nephrectomy is never indicated, as the condition is practically always bilateral. Still, unilateral cases have been reported. Osler,[10] reviewing the work of Ritchie and Lejars, found three cases of unilateral polycystic kidney in 150 cases of that condition.

---

[8] Rovsing: Treatment of Multilocular Kidney Cystoma (Congenital Cystic Kidney) by Means of Multiple Punctures, Am. J. Urol. **8**:120, 1912.

[9] Lund, F. B.: Rovsing's Operation for Congenital Cystic Kidney, J. A. M. A. **63**:1082 (Sept. 26) 1914.

[10] Osler, William: On Diagnosis of Bilateral Cystic Kidney, Am. Med. **3**:463 (March 22) 1902.

LEAD POISONING IN INFANCY *

L. EMMETT HOLT, Jr., M.D.
BALTIMORE

Poisoning by lead is a rare occurrence in early life, and is, therefore, seldom considered as a diagnostic possibility in young children. Although much has been written on the subject as it concerns older children, particularly in Australia, the condition is very rare in infants. The following case is reported because of the extreme youth of the patient and the unusual mode of poisoning.

REPORT OF CASE

History.—A baby girl, aged 8 months, was admitted to the medical service of the Babies' Hospital, April 2, 1922, because of convulsions which had begun six hours previously. The birth and early history were negative. The child had been breast fed continuously until five days before admission when a small supplementary feeding was added. For two months a slight pallor of the skin had been noted. An iron tonic had been given on this account; but it caused a digestive upset and was, therefore, discontinued. The child seemed well until the day before she was brought to the hospital. It was then noticed that she was fretful and whined most of the time. The following day convulsions occurred which were clonic in character and, according to the mother's observation, involved the right side more than the left. The convulsions were prolonged, the exact duration being unknown. On admission to the hospital they had ceased entirely.

Examination.—The child was rather pale and appeared undernourished. She was quite fretful when handled. The head showed well marked evidences of rickets: definite craniotabes, prominent frontal and parietal bosses, and a large fontanel which was full and tense. There was a staring expression in the eyes, and the pupils were dilated and reacted sluggishly to light. A slight right-sided facial weakness was noticeable when the baby cried. The deep reflexes were all exaggerated, and at times a Babinski reflex was obtained. There was a transient spasticity of the legs, but no Kernig's sign. There was also a suggestive Trousseau's sign in the right arm. A most striking phenomenon, however, was a continuous paddling motion of the arms, which were turned over and over as in the test for adiadokokinesis. There was no fever.

A lumbar puncture revealed clear fluid under apparently normal pressure, 12 cells to each cubic millimeter (95 per cent. mononuclears), a faintly positive globulin reaction (Noguchi's reagent), and a positive sugar reduction.

The electrical reactions were: CCC = 1.4 milliamperes; COC = 4.5 milliamperes; ACC = 2.0 milliamperes, and AOC = 4.0 milliamperes.

In view of the presence of rickets, the suggestive Trousseau's sign, the increased electrical excitability and the negative lumbar puncture findings, the case was regarded as one of tetany. An examination of the blood revealed a moderate anemia: erythrocytes, 3,800,000, and hemoglobin, 67 per cent.

Course.—There was no recurrence of the convulsions within the next twenty-four hours, and the mother was allowed to take the child home. The following day a film had formed in the spinal fluid, and a careful search was made for tubercle bacilli, with negative results.

---

* Received for publication, Jan. 31, 1923.

* From the Babies' Hospital of the City of New York.

The child had been home for only two days when she was brought back to the hospital because of a return of the convulsions. For a day she had remained quiet and drowsy; but then repeated attacks of general convulsions developed. In the intervals between these she appeared quite stuporous, although she continually rolled her head and moved her arms as before.

Second Examination.—On admission, no definite change in the nervous symptoms was noted. The spinal fluid, however, showed a marked increase in pressure. It contained 30 cells per cubic millimeter, 90 per cent. mononuclears, and showed a strongly positive globulin reaction.

Cutaneous tuberculin tests and a Wassermann test of the blood gave negative results. The blood count showed, in addition to the anemia noted previously, a leukocytosis of 18,400, with 58 per cent. polymorphonuclears. In the smear, however, besides a moderate degree of anisocytosis and poikilocytosis and many nucleated red cells, there were found an astonishingly large number of red cells showing basophilic stippling, many of these being present in each field.

This finding led to the suspicion of lead poisoning as a cause of the nervous symptoms. On inquiry, however, no possible source of lead could be discovered. The child had no teeth, had sucked no painted toys, had never been in freshly painted rooms, nor had she been given water which had come through lead pipes. Hereditary lead poisoning was considered; but no evidence of lead poisoning could be found in the mother. Her gums showed no lead line, and, except for a mild secondary anemia, her blood was negative. One of the mother's breasts, however, exhibited a mild eczema. It developed later that this condition had been more severe, and that for eight weeks previous to the child's illness she had been using an ointment on it. This ointment had been applied continuously, except when the child was actually nursing. It was then wiped off, to be reapplied immediately afterward. The ointment was a proprietary "diachylon compound" ointment, the chief constituent of which was lead acetate. The explanation of the poisoning in the child was thus perfectly clear.

Subsequent Course.—The child's convalescence was very slow and was complicated, successively, by otitis media, prolonged diarrhea and pyelitis. She was kept in the hospital eight weeks, until these conditions had disappeared. An attempt was made to demonstrate lead in the urine in the second week of the disease, but this was unsuccessful. No specific therapy directed toward the elimination of lead was attempted, the only medication being calcium bromid given to control the convulsions, which recurred at intervals for about a week. The automatic movements were present at times during the following four weeks, after which they were not observed. Stippled cells in the blood were present in large numbers only in the first week of the disease, after which they could be found but rarely.

Two later examinations of the spinal fluid revealed a gradual diminution in pressure and in the cell count. The last one, made four weeks after the onset, disclosed but 5 cells to each cubic millimeter, all lymphocytes. A strongly positive globulin reaction still persisted.

At the time of discharge from the hospital, the child was entirely free from active nervous symptoms, although she seemed mentally below par, recognizing neither her mother nor her bottle at the age of 10 months. During the seven months since her discharge, there has been steady improvement. Her weight has increased from 12 to 22 pounds (5.4 to 10 kg.). She now sits up, laughs, plays, recognizes people about her as well as her food, and attempts to walk, although she cannot walk alone. She does not talk. At the present time it seems impossible to determine whether the slightly retarded development is due to a cerebral lesion or is merely a result of the child's long illness.

COMMENT

It is not the purpose of the present article to review the entire subject of lead poisoning, even as it concerns children. As far as clinical descriptions of the disease are concerned, the early writings of Tanquerel[1] have yet to be improved upon. This author recognized the major symptoms of colic and constipation, anemia and wasting, neuritis with pain or paralysis, and a variety of cerebral disorders which he grouped under the term "encephalopathy." Under the last heading are described delirious forms, convulsive types, comatose varieties and a smaller number of cases with automatic movements, resembling very closely those observed in the case reported above. The more recent reports[2] of cases of lead poisoning in children have emphasized that in only two particulars does the symptomatology differ from that found in the adult: namely, the more frequent occurrence of foot-drop than wrist-drop, and the greater incidence of cerebral complications in children. The comparatively recent study of eyegrounds,[3] blood[4] and spinal fluid[5] has demonstrated characteristic changes in these tissues due to lead, and has greatly facilitated the diagnosis of this disease.

The authors quoted, however, have little or nothing to say about the occurrence of lead poisoning in early infancy, and it is the purpose of this report to draw attention to this phase of the subject.

The number of authentic cases of lead poisoning in young infants is very small. Much has been written on congenital lead poisoning, particularly by Arlidge[6] in England and Constantin Paul[7] in France. These writers made extensive studies of the families of workers in lead. In many instances, both parents were suffering from lead poisoning. Both Arlidge and Paul found in the communities studied a very high percentage of stillbirths, and also a high mortality from convulsions in the first three years of life. The number of mental defectives among the older children was likewise very large.

---

[1] Tanquerel: Lead Diseases (translation by Dana, 1848).

[2] Gibson, Love, Hardie, Bancroft, Turner: Tr. Intercolonial Medical Congress of Australasia, 1892, p. 76. Gibson: Australasian M. Gaz., 1897, p. 479. Turner: Ibid., 1897, p. 475. Gibson: Ibid., 1904, p. 149. Gibson: Tr. Australasian M. Cong. **2**:750, 1911. Brienl and Young: Ann. Trop. M. & Parasitol. **8**:475, 1914. Berger: Berl. klin. Wchnschr., 1874. Loewy: Wien. med. Press, 1883. Plate: München. med. Wchnschr. **60**:2343, 1913. Stephenson: Lancet, 1898. Stewart: Am. J. M. Sc., 1895, pp. 288, 294; Med. News, 1887. Thomas, H. M., and Blackfan, K. D.: Recurrent Meningitis, Due to Lead, in a Child of Five Years, Am. J. Dis. Child. **8**:377 (Nov.) 1914. Blackfan, K. D.: Am. J. M. Sc. **153**:877 (June) 1917. Chapin: Med. Rec., 1884. Mosny and Malloizel: Rev. de méd. **27**:505, 1907. Roussel: Loire méd., 1898, p. 331. Bouchut: Gaz. d. hôp., 1875. Von Hove: Bull. Soc. de méd. de Gand., 1889, p. 151.

[3] Gibson, Brienl and Young: Footnote 2.

[4] Gravitz: Klinische Pathologie des Blutes, Leipzig, 1911.

[5] Mosny and Malloizel: Footnote 2. Gibson: Tr. Australasian M. Cong. **2**:750, 1911. Blackfan: Footnote 2.

[6] Arlidge: Ann. Pub. Health & M. Sc., translated by Beauregard, 1865, quoted by Dufour-Labastide: Thèse, Paris, 1896.

[7] Paul, Constantin: Arch, gén. de méd., 1860.

Only a few reports could be found in the literature in which the placental transmission of lead was beyond question. Ganyaire [8] demonstrated the presence of lead in the placenta, liver and brain of an infant dying when 48 hours old. Legrand and Winter [9] report a similar case.

Paul admits that, in many cases which he has classed as congenital, the poisoning may have continued after birth through the mother's milk. Furthermore, Balland [10] was able to recover considerable quantities of lead from the milk of a mother suffering from lead poisoning. The statistical observations of Arlidge and Paul cannot be considered as altogether reliable, since no sharp line can be drawn between the cases of congenital and acquired lead poisoning. The evidence is wanting that congenital lead poisoning is a frequent occurrence.

A somewhat larger number of reliable reports of acquired lead poisoning in infancy were found. Dufour-Labastide [11] has collected a series of cases of lead poisoning in children, fourteen of whom were under 2 years of age, and one but 3 weeks old. In these cases, there was a great variety in the sources of the lead. In only one was the poison introduced by inhalation of dust which contained lead. In the others it was introduced by mouth, in paint from toys, in buns and candies colored with lead chromate; in printers' type, ointment of lead oxid (litharge), water and milk which had stood in lead receptacles. Improper medication was responsible for two cases. In three cases, the child obtained the poison from the mother: one by sucking paint from the mother's face, and two (reported by Von Hove [12] and Bouchut [13]) by nursing following the use of a lead ointment on the mother's breast. I have found only one other reference to a similar source of ingestion. Roussel [14] reports a small epidemic of lead poisoning in infants, the result of a lead acetate ointment prescribed for the breasts of nursing mothers by a druggist.

It is generally conceded that cases of lead poisoning showing cerebral involvement are more liable to be fatal. In comparing the mortality of such cases in infants with that in older children, it is surprising to find a low mortality among infants. In Dufour-Labastide's small series four out of six patients with cerebral symptoms recovered. The statistics for older children differ widely. Stewart[15] reports a mortality of six out of seven children with convulsions. Holt and Howland[16] observed only one recovery out of eight cases, and Berger[17] reports nine fatal cases in a single family. The Australian writers, Gibson, Love and Turner, however, find a mortality of from 15 to 20 per cent. The prognosis in these cases seems to depend in large measure upon the success with which lead can be eliminated from the diet. While this is sometimes very easy, it is in other cases next to impossible. This variable factor may account for the discrepancies reported among older children.

---

[8] Ganyaire: Thèse de Paris, 1900.

[9] Legrand and Winter, quoted by Dufour-Labastide: Thèse de Paris, 1902.

[10] Balland: Thèse de Paris, 1896.

[11] Dufour-Labastide: Thèse de Paris, 1902.

[12] Von Hove: Footnote 2.

[13] Bouchut: Footnote 2.

[14] Roussel: Loire méd., 1898, p. 331.

The case reported shows that lead poisoning should be considered as a diagnostic possibility at any age, when dealing with convulsions of obscure origin, even though no source of poisoning is evident.

---

[15] Stewart: Am. J. M. Sc., 1895, p. 294.

[16] Holt, L. E., and Howland, J.: Diseases of Infancy and Childhood, Ed. 8, New York, D. Appleton & Co., p. 726.

[17] Berger: Footnote 2.

TYPES OF ORGANISM FOUND IN A SERIES OF TUBERCULOUS CHILDREN *

J. KEITH GORDON, M.D., AND ELSIE W. BROWN, B.Sc.

BOSTON

In view of the fact that a determination of the relative frequency with which bovine tuberculosis occurs in children of the same community has a very definite bearing upon the nature of the milk supply of that community, and also that, in some instances, the figures of other investigators have been somewhat too small to deduce final percentages of bovine infection in children, a study of the subject was undertaken in these laboratories. It was our chief object to ascertain the type of infection in each case, rather than to attempt to discuss at any length the morphologic and cultural characteristics of tubercle bacilli from bovine and human sources.

Following the discovery by Theobald Smith,[1] in 1898, that two distinct types of tubercle bacilli could be recovered from tuberculous lesions in man, one of which was also pathogenic for cattle, and thus designated "bovine," and the other pathogenic only for human beings and, therefore, designated "human," and his demonstration of the fact that both rabbits and guinea-pigs differ in their susceptibility to these two types of bacilli, numerous workers became interested in the subject. Wolbach and Ernst,[2] and others, studied with great care and completeness the cultural characteristics and morphology of the organisms, while the largest series of actual cases of tuberculosis in this country that were classified according to type, age and parts affected appeared in the monograph of Park and Krumwiede,[3] in 1910. From a study of a large series of cases in the State of New York, and later [4] combining their figures with those of others, they pointed out that the bovine type of tubercle bacillus was the infecting agent in nearly 11 per cent. of all cases, and that of these more than 90 per cent. occurred

---

* Received for publication, Dec. 12, 1922.

* From the Laboratories of Pathology and Bacteriology, Children's Hospital and Harvard Medical School.

[1] Smith, Theobald: A Comparative Study of Bovine Tubercle Bacilli and of Human Bacilli from Sputum, J. Exper. Med. **3**:451, 1898.

[2] Wolbach and Ernst: Observations on the Morphology of Bacillus Tuberculosis from Human and Bovine Sources, J. M. Res. **10**:315, 1903.

[3] Park and Krumwiede: The Relative Importance of the Bovine and Human Types of Tubercle Bacilli in the Different Forms of Tuberculosis, J. M. Res. **23**:205, 1910.

[4] Park and Krumwiede: The Relative Importance of the Bovine and Human Types of Tubercle Bacilli in the Different Forms of Tuberculosis, J. M. Res. **27**:109, 1912-1913.

in children under 16 years of age. They also showed that the bovine virus caused somewhat less than 10 per cent. of the total deaths in children.

Much more startling results have been obtained by British investigators. Mitchell,[5] in a study of seventy-two cases of tuberculous adenitis in children, in and about the city of Edinburgh, found that 90 per cent. of the total number were infected with a bovine organism, while Fraser,[6] in a series of seventy cases of bone and joint tuberculosis at the Sick Children's Hospital, Edinburgh, recovered the bovine organism in nearly 60 per cent. of the total. The former emphasized the almost universal practice of feeding Scottish children with unsterilized cow's milk, and the great prevalence of tuberculosis in the dairy cows of Scotland, combined with the inadequate veterinary inspection.

I. TECHNIC

It is generally conceded that in order to establish definitely the identity of the human and bovine types of tubercle bacillus, the organisms must not only show characteristic types of growth on artificial culture mediums, but must also be tested for their virulence. The latter, which is the most conclusive means of differentiation, depends upon the extent of the lesions produced in rabbits inoculated with the bacilli, while the nature of the growth of the organisms upon egg mediums appears to give sufficient contrast to enable one to distinguish the two types culturally. Some workers have, in addition, employed the "Smith reaction,"[7] which consists of noting the constant curve of acid reduction which the two types produce when grown upon slightly acid glycerin bouillon; but its practical usefulness appears to be interfered with by the length of time that must elapse before a final reaction is obtained. In the main, the variation in technic used by different workers has existed simply in the method chosen for inoculation of rabbits. Since this fact alone may slightly alter the picture of the findings, we have considered that a somewhat detailed account of the routine procedure that we have employed in each case might not be out of place here.

The material to be tested was ground up with about 10 c.c. of sterile saline in a sterile mortar. After complete disintegration, the supernatant fluid was decanted into another sterile vessel, whence it was drawn up into a 5 c.c. syringe. Two rabbits and two guinea-pigs of known weight were inoculated with 1 c.c. of this fluid, the injection being made subcutaneously into the groin in the case of one guinea-pig and one rabbit, while the other guinea-pig and rabbit were inoculated intraperitoneally. The animals were then placed in clean cages in a room separate from that in which the inoculations and dissections were made, and their weights recorded weekly. If any marked loss of weight occurred in the guinea-pigs during the two weeks subsequent to inoculation, the animals were killed in order to obviate postmortem contamination, since it is difficult to obtain a sterile culture from an animal after death from tuberculosis. Guinea-pigs that did not show any marked loss of weight were allowed to live, as a maximum, four weeks from the time of inoculation. The weight of these animals is not always a reliable sign of infection, since some showed a gain in weight even when there was generalized tuberculosis. Small guinea-pigs are the least resistant, and lesions appear earlier in them than in the larger ones. The picture of virulence in guinea-pigs is not so marked as to be of value in the differentiation of the two types of bacilli; as a rule, however, the bovine type of organism causes a more generalized tuberculosis than the human. Constant findings in all cases were, in the event of an intraperitoneal inoculation, a tumor of the omentum, and, in the case of subcutaneous inoculation in the groin, caseation of the inguinal and retroperitoneal lymph nodes, while, in both instances, there were gross tubercles in the spleen.

---

[5] Mitchell, A. P.: Report on the Infection of Children with the Bovine Tubercle Bacillus, Brit. M. J. **1**:125, 1914.

[6] Fraser, J.: A Study of the Types of Organism in a Series of Bone and Joint Tuberculosis of Children, Brit. M. J. **1**:160, 1913.

[7] Smith, Theobald: The Reaction Curve of Tubercle Bacilli from Different Sources in Bouillon Containing Different Amounts of Glycerin, J. M. Res. **13**:405, 1904-1905.

Rabbits were killed within the minimum period of six weeks. Here again the weight of the animals is not always a reliable sign, although a constant gain practically precludes the presence of the bovine virus. In these animals, the contrast in the anatomic picture was particularly striking. Those inoculated subcutaneously in the groin with a suspension of the human type of organism showed, in the majority of cases, no gross evidence of tuberculosis, although occasionally there was a caseous nodule at the site of inoculation; while, in the case of the bovine virus, there was tuberculosis with caseation of the inguinal and retroperitoneal lymph nodes, the lungs and spleen being in most cases riddled with tubercles. Intraperitoneal inoculation of the human virus, in the majority of instances, revealed no gross evidence of tuberculosis, although in many instances a caseous nodule appeared at the site of inoculation, or a small caseous mesenteric lymph node, and, in some instances, a few scattered tubercles in the lungs. In the case of the bovine type of organism, there was a large caseous area at the site of inoculation, a large omental mass, and miliary tubercles in the peritoneum, lungs and spleen.

Cultures were taken from the killed guinea-pigs in the following manner: The animal was skinned, care being taken not to contaminate the body cavities. It was then strapped or pinned to a board, and, with a searing knife, a longitudinal sear was made from the top of the sternum to the symphysis pubis, and two diagonal sears, one just above the symphysis pubis and the other just below the costal border. By cutting along these sears with a sterile instrument, the body cavities were exposed aseptically. Pieces of tuberculous tissue were then excised under sterile precautions and placed in a petri dish, where they were thoroughly disintegrated before being transferred to artificial culture mediums. In the choice of tissue for cultural purposes, we have preferred regional lymph nodes, as we have found them less prone to contamination by molds than other organs. In the case of animals inoculated in the groin, two constantly affected and readily accessible nodes are those which are situated behind the peritoneum, in the region of the bifurcation of the iliac vessels.

Small pieces of the disintegrated tissue were rubbed thoroughly over the surface of at least ten tubes of Dorset's egg medium, both with and without glycerin. We found that our most successful cultures were obtained from those tubes from which the pieces of tissue were removed immediately after inoculation, the retention of the tissue seeming to encourage the appearance of molds and to have a slight inhibitory effect on the growth of the tubercle bacillus.

Since we were not concerned with a detailed study of the morphology and physiology of the organisms, we took notice only of such gross characteristics of the cultures as might serve to differentiate the growth of the human and bovine types of tubercle bacillus. In fact, in our primary cultures on the mediums used, the morphology of the two types of bacilli was not distinctive enough to be of diagnostic value, although, in the main, the organisms of the human type took a less heavy stain than those of the bovine type and were inclined to be more curved.

We found that the majority of cultures taken from material that was not virulent for rabbits, and which we, therefore, designated as belonging to the "human" type, showed the following characteristics:

1. The growth on plain egg and on glycerin egg medium was equally luxuriant.

2. This growth was macroscopically apparent in from ten days to three weeks.

3. The colonies were dry and "crumby," and, in some of the older cultures, they showed a slight buff pigment.

On the other hand, the majority of cultures from material which gave a generalized tuberculosis to rabbits, and which we called "bovine," showed these characteristics:

1. This type of organism grew on glycerin egg in only two cases and then very scantily.

2. On plain egg, it grew in almost every case, but with varying degrees of luxuriance. In no case did it grow as heavily as the human type.

3. Growth in these cultures was not, as a rule, macroscopically evident before an incubation period of three weeks.

4. The colonies were moist and flat and tended to be more confluent than those of the human type.

In a few cases we failed to obtain growth in the cultures. This lack of success was quite definitely traced to the use of poor lots of mediums and to the presence of contaminating organisms. Several cultures planted from tuberculous material of the human type, according to the animal tests, showed a moist growth similar to that of the bovine organism. In these instances, it was noticed that the tissue used for inoculation was inclined to be soft and somewhat puriform, as compared with the dry caseous material used for the more heavily growing cultures.

These observations were all made on the primary cultures from infected animal tissue. Later generations of cultures were not suitable for differential diagnosis, since the more robust of the bovine cultures began to assume the dry appearance of the human type even in the second or third generation.

Because of the various environmental factors concerned in the cultivation of the tubercle bacillus, we believe that our cultures, while valuable in checking the results of animal inoculations, were not reliable enough in themselves for determining the type of tuberculous infection.

II. CLINICAL AND PATHOLOGIC DATA AND TYPES OF ORGANISM RECOVERED

Our own series of cases has been selected from material in the wards of the Children's and Infants' hospitals, Boston, and consists of thirty tuberculous children, ranging in age from 4 months to 11 years, all of whom resided in the Boston district. We have given a summary of the history and clinical and pathologic findings, together with the type of organism recovered in each case, in order to attempt to establish a definite relationship between the type of organism and such factors as contact with tuberculous adults, the nature of the child's food and the extent of the lesions.

REPORT OF CASES

CASE 1.—A. S., boy, aged 4 months, was admitted to the Infants' Hospital, March 15, 1922, with a history of cough and upper respiratory symptoms for two months previous to admission. Vomiting and diarrhea had been evident for some time since then. There had been retraction of the head for three weeks. The baby was breast fed. The father had a cough and had lost weight for one year; but there was no definite family history of tuberculosis or exposure to it. Physical examination revealed marked malnutrition, retraction of the head and positive Kernig and Brudzinski signs, and fine râles over both lungs. The Pirquet reaction was positive. The spinal fluid was cloudy, contained 130 cells per cubic millimeter; and acid-fast bacilli. A roentgenogram of the chest revealed marked bilateral infiltration, with a cavity at the left apex. The child died March 19, 1922. Necropsy revealed tuberculous pneumonia and generalized miliary tuberculosis, with involvement of the meninges, the primary focus being the left apex. The human type of organism was recovered.

Case 2.—M. M., girl, aged 4 months, was admitted to the Infants' Hospital, Jan. 12, 1922, with a history of fever, anorexia and failure to gain during the previous three weeks. The family history was negative, and there was no history of exposure to tuberculosis. The baby had been breast fed until the illness began. Physical examination revealed definite evidence of consolidation of the right lung in the axilla, with scattered râles throughout both sides of the chest. Some meningeal signs were present. The Pirquet reaction was positive. The roentgen ray revealed extensive tuberculous processes throughout both lungs, The spinal fluid contained 100 cells per cubic millimeter; small lymphocytes, 71 per cent., and no micro-organisms were found. The child died, Jan. 18, 1922. Necropsy revealed tuberculous bronchopneumonia with generalized miliary tuberculosis and tuberculous meningitis. The human type of organism was recovered.

Case 3.—J. F., boy, aged 4 months, was admitted to the Infants' Hospital, June 5, 1922, with a history of irritability, refusal to take food, sleeplessness and sighing respirations. Drowsiness and slight cough had been present for eight days previous to admission. The baby was breast fed. The family history was negative, and there was no history of exposure to tuberculosis. Physical examination revealed marked prostration and emaciation, rapid. shallow breathing, a bulging anterior frontanel, and bilateral internal strabismus. The lungs showed signs of consolidation in the left upper lobe, and diffuse pulmonary tuberculosis, confirmed by the roentgen ray. Kernig's sign was positive, as was also the Pirquet reaction. The spinal fluid showed 580 cells; 60 per cent. polymorphonuclears, and numerous acid-fast bacilli. The infant died, June 7, 1922. Necropsy revealed tuberculous pneumonia, tuberculous meningitis and generalized miliary tuberculosis. The human type of organism was recovered.

Case 4.—V. L., girl, aged 5 months, for whom there are no available records as to history or physical examination, was treated with a clinical diagnosis of tuberculous meningitis. No necropsy was obtained. The human type of organism was recovered.

Case 5.—W. F., boy. aged 6 months, was admitted to the Infants' Hospital, May 23, 1922, with a history of gradual onset of drowsiness, vomiting and convulsions, commencing five days before admission. There was a definite family history of tuberculosis and of exposure to it. The infant was breast fed. Physical examination revealed enlarged cervical glands on both sides and signs of meningitis. The skin showed tuberculid rash. The Pirquet reaction was positive. The roentgen ray revealed diffuse pulmonary tuberculosis, with thickening of the hilum and paratracheal involvement. The spinal fluid contained 359 cells, the majority of which were mononuclears, and positive albumin and globulin. The patient died, June 1, 1922. No necropsy was obtained. Clinical diagnosis was generalized miliary tuberculosis and tuberculous meningitis; type of organism, human.

Case 6.—J. M., boy, aged 8 months, was admitted to the Infants' Hospital, April 7, 1922, with a history of pneumonia complicated by pleurisy, six weeks before admission. The day before admission the child had become very irritable and commenced to vomit. The family history was negative, and there was no history of exposure to tuberculosis. The infant had been bottle fed since birth. Physical examination revealed signs of meningitis and consolidation of the apex of the left lung, with diffuse râles and impaired resonance throughout. There was a tuberculid rash on the skin. The Pirquet reaction was positive. A roentgenogram of the chest revealed diffuse pulmonary tuberculosis. The spinal fluid was under pressure and contained 46 cells per cubic millimeter, all lymphocytes. The patient was taken home, April 9, 1922. The clinical diagnosis was: generalized miliary tuberculosis and tuberculous meningitis; type of organism, human.

Case 7.—J. G., boy, aged 10 months, was admitted to the Infants' Hospital, Jan. 5, 1922, with a history of cough and fever for three weeks. There was a definite history of exposure to tuberculosis for two months. Physical examination revealed marked anemia and signs of consolidation in both lungs. The Pirquet reaction was positive. Pulmonary lesions finally involved both lungs to a marked degree. The child died, Jan. 31, 1922. Necropsy revealed tuberculous bronchopneumonia and generalized miliary tuberculosis. The brain and meninges were negative. The human type of organism was recovered.

Case 8.—A. A., boy, aged 10 months, was admitted to the Infants' Hospital, May 7, 1922, with a history of vomiting for three days. The family history was negative, and there was no history of exposure to tuberculosis. The child was breast fed. Physical examination revealed irritability and marked loss of weight. Râles were heard throughout both lungs. Several scattered erythematous nodules were present on the skin, some of which showed breaking down. An excised nodule showed tuberculosis of the skin, and tubercle bacilli were demonstrated in the tissue. The Pirquet reaction was positive. The roentgen ray revealed diffuse tuberculous involvement of both lungs. The spinal fluid contained 90 cells, the majority of which were mononuclears, positive albumin and globulin and acid-fast bacilli. The patient was taken home, May 9, 1922. The clinical diagnosis was generalized miliary tuberculosis and tuberculous meningitis; type of organism, bovine.

Case 9.—M. F., boy, aged 12 months, was admitted to the Infants' Hospital, Feb. 21, 1922, with a history of cough, some fever, and loss of weight for three months previous to admission. One month before admission, he had an acute illness lasting ten days, which the physician had said was bronchopneumonia. Since that time, loss of weight, fever and perspiration had been noted. He was breast fed for four months, then he was given a milk mixture. The family history was negative, and there was no history of exposure to tuberculosis. Physical examination revealed consolidation of almost the entire left lung. The roentgen ray revealed consolidation, not typically tuberculous. The Pirquet reaction was positive. The patient died suddenly, March 9, 1922. Necropsy revealed tuberculous bronchopneumonia and generalized miliary tuberculosis. An examination of the head was not permitted. The human type of organism was recovered.

Case 10.—T. P., boy, aged 13 months, was admitted to the Infants' Hospital, April 29, 1922, with a history of fever and cough, commencing three months previously, and recurrent fever ever since. Three days before admission he became irritable, and jerky movements of the extremities developed. The family history was negative, and there was no history of exposure to tuberculosis. The child was breast fed for eight months, then put on a milk mixture. Physical examination revealed irritability and emaciation. The Pirquet reaction was positive. The spinal fluid contained 39 cells per cubic millimeter, mostly mononuclears and acid-fast bacilli. Tests for albumin and globulin were positive. The patient died, May 14, 1922. Necropsy revealed generalized miliary tuberculosis, including the heart and pancreas, and tuberculous meningitis of alimentary origin. The bovine type of organism was recovered.

Case 11.—C., girl, aged 14 months, was admitted to the Infants' Hospital, June 2, 1922, with a history of vomiting and listlessness for two months previous to admission. The family history was negative, and there was no history of exposure to tuberculosis. She had been fed cow's milk occasionally since 1 year of age. Physical examination revealed marked prostration and drowsiness. The Pirquet reaction was questionable. The spinal fluid contained 87 cells per cubic millimeter, and large numbers of acid-fast bacilli. Tests for albumin and globulin were positive. Roentgenographic examination of the chest revealed miliary tubercles in the lungs. The child died, June 11, 1922. Necropsy revealed generalized miliary tuberculosis and tuberculous meningitis, of respiratory origin. The human type of organism was recovered.

Case 12.—J. T., boy, aged 16 months, was admitted to the Infants' Hospital, March 22, 1922, with a history of cough and fever for three weeks previous to admission. He was breast fed for two months, then he was put on a milk mixture. The family history was negative, and there was no history of exposure to tuberculosis. Physical examination revealed signs of diffuse bronchopneumonia. The Pirquet reaction was positive. Tubercle bacilli were found in the spinal fluid. The patient died, March 25, 1922. Necropsy revealed generalized miliary tuberculosis and tuberculous meningitis, of respiratory origin. The human type of organism was recovered.

Case 13.—M. G., girl, aged 18 months, was admitted to the Infants' Hospital, May 16, 1922. She had developed a cold and cough, ten weeks before admission. The cough had continued, with slight fever at times. Convulsions had occurred four days before admission, followed by drowsiness and rigidity. There was a history of loss of weight, poor appetite and profuse sweating. She had been in close contact with the father who had active pulmonary tuberculosis. Physical examination revealed areas of impaired resonance in the lungs and râles throughout. The Pirquet reaction was positive. The spinal fluid contained 260 cells, mostly mononuclears and acid-fast bacilli. Tests for albumin and globulin were positive. Acid-fast bacilli were found in the sputum. The patient died, May 18, 1922. Necropsy revealed generalized miliary tuberculosis and tuberculous meningitis, of respiratory origin. The human type of organism was recovered.

Case 14.—C. L., boy, aged 18 months, was admitted to the Infants' Hospital, April 15, 1922, with a history of gradual onset of sleepiness, irritability and vomiting, commencing ten days before admission. The family history was negative; but there was a definite history of the patient's having visited a tuberculous family for long periods of time. The child was breast fed for three months. Physical examination revealed bronchial breathing over the left scapula, but no definite signs of meningitis. The Pirquet reaction was positive. The spinal fluid contained 127 cells per cubic millimeter, the majority of which were mononuclears, and acid-fast bacilli. The patient was taken home, April 28, 1922. He died two days later. The clinical diagnosis was: generalized miliary tuberculosis. and tuberculous meningitis; type of organism, human.

Case 15.—J. C., boy, aged 2 years and 2 months, was admitted to the Children's Hospital, Oct. 17, 1921. Ten days before admission he had become feverish and drowsy. Four days later he commenced to vomit. Two days before admission, he had a generalized convulsion. Irregular temperature, as high as 101 F., had been noted since the onset. The family history was negative, and there was no history of exposure to tuberculosis. Physical examination revealed definite signs of meningitis. The spinal fluid contained 55 cells, 84 per cent. of which were mononuclears. The child died, Oct. 18, 1921. Necropsy revealed generalized miliary tuberculosis and tuberculous meningitis, of alimentary origin. The bovine type of organism was recovered.

Case 16.—F. G., boy, aged 2 years and 3 months, was admitted to the Children's Hospital, March 20, 1922. He had been treated in the orthopedic service during the previous year for tuberculosis of the spine. One week before admission, he commenced to vomit and continued to do so up to time of admission. The family history was negative, and there was no history of exposure to tuberculosis. Physical examination revealed definite meningeal signs and evidence of miliary tuberculosis. The spinal fluid was under pressure and contained 500 cells per cubic millimeter, the majority of which were mononuclears, and acid-fast bacilli. The child died, March 26, 1922. No necropsy was obtained. The clinical diagnosis was: generalized miliary tuberculosis and tuberculous meningitis; type of organism, human.

Case 17.—R. G., boy, aged 2 years and 8 months, was admitted to the Children's Hospital, March 13, 1922, with a history of diarrhea lasting for two weeks, five months previous to admission. Since that time, anorexia and marked loss of weight had been noted. The family history was negative, and there was no history of exposure to tuberculosis. Physical examination revealed the typical tuberculous habitus; signs of fluid in the flanks and a questionable mass in the right flank. Roentgenographic examination of the chest revealed miliary tubercles in the lungs. The Pirquet reaction was negative. The child died, March 19, 1922. Necropsy revealed generalized miliary tuberculosis of alimentary origin. An examination of the head was not permitted. The bovine type of organism was recovered.

Case 18.—P. K., boy, aged 3 years and 2 months, was admitted to the Children's Hospital, May 13, 1922, with a history of tonsillectomy in December, 1921. Two weeks before admission he commenced to vomit. This was followed by a headache and drowsiness. The family history was negative, and there was no history of exposure to tuberculosis. Physical examination revealed stiffness of the neck and a positive Brudzinski sign. The spinal fluid was clear, under pressure, and contained 300 cells, all of which were mononuclears. Two days later, the child developed definite signs of meningitis. Tubercle bacilli were found in the spinal fluid. He died, May 9, 1922. Necropsy revealed generalized miliary tuberculosis and tuberculous meningitis, respiratory in orgin. The human type of organism was recovered.

Case 19.—K. H., girl, aged 3 years and 2 months, was admitted to the Children's Hospital, March 4, 1922. Two weeks before admission, she became feverish and lost her appetite. During the five days previous to admission she had severe headache, and the temperature ranged from 100 to 102 F. The family history was negative, and there was no history of exposure to tuberculosis. The physical examination revealed stiffness of the neck. The Pirquet reaction was positive. Signs of meningitis gradually developed after admission. The spinal fluid contained 400 cells per cubic millimeter, all lymphocytes, and acid-fast bacilli. The child died, March 14, 1922. No necropsy was obtained. The clinical diagnosis was: tuberculous meningitis; type of organism, human.

Case 20.—A. R., boy, aged 3 years and 5 months, was admitted to the Children's Hospital, March 2, 1922, with a history of sore throat, six weeks before admission, followed by swelling of the glands of the left side of the neck. The mother died when the patient was born, otherwise the family history was negative. There was no history of exposure to tuberculosis. The glands, tonsils and adenoids were excised, March 3, 1922. The glands and both tonsils showed tuberculosis. He was discharged, March 12, 1922. The diagnosis was; tuberculous adenitis and tuberculosis of the tonsils; type of organism, bovine.

Case 21.—K. M., boy, aged 4 years and 4 months, was admitted to the Children's Hospital, April 26, 1922, with a history of loss of weight, loss of appetite and night sweats during the six months previous to admission. During the three weeks before admission he had been coughing, and the temperature had varied between 99 and 100 per cent. The family history was negative, and there was no history of exposure to tuberculosis. Physical examination revealed presence of fluid in the left pleural cavity. The Pirquet reaction was positive. Fluid was aspirated from the chest. The patient was discharged home improved, May 1, 1922. The clinical diagnosis was: pulmonary tuberculosis; type of organism, human.

Case 22.—T. C., boy, aged 4 years and 5 months, was admitted to the Children's Hospital, Feb. 23, 1922. He had had nasopharyngitis, bronchitis and digestive disturbances since birth. Six days before admission he became feverish and commenced passing bloody urine. The family history was negative, and there was no history of exposure to tuberculosis. Physical examination revealed marked emaciation, enlarged tonsils, and enlarged cervical nodes on both sides. Two weeks after admission he had a convulsion lasting for three hours. Two weeks after this, he became drowsy, and signs of meningitis developed. The Pirquet reaction was positive. The spinal fluid contained 390 cells, chiefly mononuclears, and acid-fast bacilli. The patient was taken home. Feb. 29, 1922. The clinical diagnosis was: tuberculous meningitis; type of organism, human.

Case 23.—W. G., boy, aged 6 years, was admitted to the Children's Hospital, April 24, 1922, with a history of limp, commencing eighteen months before admission. He was treated with a plaster cast and later an abduction splint. Six weeks before admission the hip began to swell. The family history was negative, and there was no history of exposure to tuberculosis. Physical examination revealed flexion and abduction of the left hip, and a large fluctuating swelling in the left upper thigh. The latter was incised and drained, April 28. The clinical diagnosis was: tuberculosis of the hip joint; type of organism, bovine.

Case 24.—E. W., girl, aged 7 years, was readmitted to the Children's Hospital, April 7, 1922, having been treated in this hospital, three years previously, for tuberculosis of the hip-joint. One week before admission, she began to have headache. During the four days previous to admission, she had vomited continuously. Marked irritability and slight rise of temperature had been noted. The family history was negative, and there was no history of exposure to tuberculosis. Physical examination revealed definite signs of meningitis and bilateral choked disks. The spinal fluid was clear, and under pressure. It contained 150 cells per cubic millimeter, and acid-fast bacilli. The patient died, April 14, 1922. No necropsy was obtained. The clinical diagnosis was: tuberculous meningitis; type of organism, human.

Case 25.—A. V., boy, aged 8 years and 4 months, was admitted to the Children's Hospital, Oct. 3, 1921, with a history of tonsillectomy, three weeks before admission, followed by general malaise and dull pain in the left side of the abdomen. A younger sister had been previously treated in this hospital for tuberculosis of the hip-joint. On examination under ether, a fairly large movable mass could be felt in the right lower abdomen. The Pirquet reaction was positive. Operation was performed, October 5, and the appendix and inflammatory tissue removed, the latter being diagnosed as tuberculosis. The patient was sent to a convalescent home. He was readmitted, March 5, 1922, and examination revealed a tense and distended abdomen, with signs of fluid in the flanks. March 20, 1922, signs of meningitis appeared. The patient died, March 31, 1922. No necropsy was obtained. The clinical diagnosis was: tuberculous meningitis and tuberculous peritonitis; type of organism, human.

Case 26.—H. D., girl, aged 10 years and 2 months, was readmitted to the Children's Hospital, Feb. 18, 1922. She had been treated in this hospital for tuberculosis of the hip-joint, off and on, during the previous five years. The younger brother died of tuberculous meningitis in this hospital. The hip-joint was aspirated, April 23, 1922. The clinical diagnosis was: tuberculosis of the hip-joint; type of organism, bovine.

Case 27.—T. H., boy, aged 10 years and 4 months, was first admitted to the Children's Hospital, April 12, 1921, with a history of limp, commencing in August, 1920, followed by pain in right hip-joint. An aunt and grandmother had died of tuberculosis. The Pirquet reaction was positive. He was readmitted, April 14, 1922. A fluctuating abscess, pointing in the right femoral triangle was incised, May 3, 1922. The clinical diagnosis was: tuberculosis of the hip-joint; type of organism, human.

Case 28.—A. G., boy, aged 11 years, was first admitted to the Children's Hospital, March 23, 1920, with a history of frequency and bloody urination, for seven months, and loss of weight. The glands of the neck had been removed on three different occasions at other hospitals. The family history was negative, and there was no history of exposure to tuberculosis. A catheterized specimen of urine from the left kidney showed acid-fast bacilli. Nephrectomy was performed, April 12, 1920. In January, 1922, frequency of urination commenced again. Acid-fast bacilli were found in a catheterized specimen of urine. The clinical diagnosis was: tuberculosis of the kidney; type of organism, bovine.

Case 29.—M. G., girl, aged 11 years, was admitted to the Children's Hospital, March 26, 1922, with enlarged glands on the left side of the neck. The family history was negative, and there was no history of exposure to tuberculosis. The excised glands showed tuberculosis with caseation. The bovine type of organism was recovered.

In addition to the foregoing series we have studied the following case from the Peter Bent Brigham Hospital, which is interesting because of its clinical history:

Case 30.—P. M., boy, aged 14 months, was admitted to the Peter Bent Brigham Hospital, Nov. 2, 1921, with a history of gradual swelling of the glands of the neck on the left side for six months. The family history was negative, and there was no history of exposure to tuberculosis. The baby was breast fed for four months, then it was fed certified, not pasteurized, milk. The glands when excised showed tuberculosis. The bovine type of organism was recovered.

COMMENT

In the accompanying table, we have classified these thirty cases according to the method of Park and Krumwiede, which not only contributes toward uniformity but also affords a satisfactory method of grouping the cases in accordance with either the clinical or postmortem diagnosis. Permission for necropsy in all of the fatal cases was not obtained, and they are classified according to the clinical diagnosis. Among these are the cases grouped under the heading "Tuberculous Meningitis." On the other hand, in the event necropsy was not performed and the point of origin of the infection was in the alimentary tract, the cases are tabulated either under the heading "Generalized Tuberculosis, Alimentary Origin," or "Generalized Tuberculosis Including the Meninges, Alimentary Origin." Those cases classified as "Generalized Tuberculosis" or "Generalized Tuberculosis Including the Meninges" are either grouped according to (1) clinical diagnosis; (2) pathologic diagnosis, when the point of origin was in the respiratory apparatus, or (3) pathologic diagnosis, when the point of origin was in the respiratory apparatus, but when permission to examine the head was not granted.

THIRTY CASES TABULATED ACCORDING TO THE METHOD OF PARK AND KRUMWIEDE

Classification	Under Five Years		Under Twelve Years	
	Human	Bovine	Human	Bovine
Pulmonary tuberculosis	1	—	—	—
Tuberculous adenitis, cervical	—	1	—	1
Tuberculous adenitis, axiliary or inguinal	—	—	—	—
Abdominal tuberculosis	—	—	—	—
Generalized tuberculosis, alimentary origin	—	1	—	—
Generalized tuberculosis	2	—	—	—
Generalized tuberculosis, including meninges, alimentary origin	—	2	1	—
Generalized tuberculosis, including meninges	11	1	—	—
Tuberculous meningitis	3	—	1	—
Tuberculosis of bones and joints	—	—	1	2
Genito-urinary tuberculosis	—	—	—	1
Tuberculosis of skin	—	—	—	—
Tuberculosis of tonsils	—	1	—	—
Tuberculous sinus or abscess	—	—	—	—
Tuberculous mouth and cervical nodes	—	—	—	—
Sepsis, latent bacilli	—	—	—	—
Totals	17	6	3	4
Percentage of bovine infection	25		52	

SUMMARY

In a total of thirty cases of tuberculosis in children under the age of 12 years, the bovine organism was identified in ten instances, or in 33⅓ per cent. Twenty-three of the total number of patients were less than 5 years of age. In six of these, the organism was of the bovine type (or 25 per cent.). The remaining seven patients were between the ages of 5 and 16 years, and of these there were four instances of bovine infection, or 52 per cent. From these figures, it can be seen that there was a greater actual incidence of bovine infection in the children under 5 years of age, although the number of bovine cases in patients between the ages of 5 and 12 years was relatively greater. Moreover, in the infants under 1 year of age, the bovine organism was identified only in a single instance.

Twenty-two of the total number of cases were known to be fatal. Of these, four, or less than 20 per cent., were of the bovine type. Permission for necropsy was obtained in twelve of the fatal cases. Of this number, the cases in which the point of origin of infection was found in the alimentary tract proved to be, without exception, bovine in type. Only one of the fatal cases (Case 25) would appear to be contradictory to this statement; but no necropsy was obtained to verify the origin of the infection. On the other hand, the human bacillus was recovered from all those cases in which the point of origin, at necropsy, was in the respiratory tract. From these facts, the conclusion is obvious.

In five cases out of the total number, the history indicated that the children were exclusively breast fed. The reliability of this statement on the part of the parents may be regarded as doubtful, for although four of this number showed a human type of infection, the bovine organism was recovered in one instance. Since in the latter case (Case 8), the patient was 10 months old, it would seem fairly reasonable to assume that, in addition to the breast, there had been supplementary feedings of cow's milk, although this has been denied by the mother. In Case 30 there was a very definite and reliable history of the baby's being fed exclusively with "certified," not sterilized, milk, since weaning. This history was verified by tracing the source of the infection to the herd which supplied the milk.

Seven cases of the total number gave a definite history of either familial tuberculosis or contact with tuberculous persons. Six of these proved to be infected with the human and one with the bovine organism. In the latter instance, the patient had been exposed to a younger brother who had previously died of generalized tuberculosis.

In consideration of the fact that the foregoing figures apply to only thirty cases of tuberculosis in infancy and childhood, no general conclusions may be reached other than that, in the Boston district, the percentage of bovine tuberculosis would appear unnecessarily high.[8]

---

[8] A further study of this subject is being conducted in these laboratories.

CALCIUM ABSORPTION IN CHILDREN ON A DIET LOW IN FAT *

L. EMMETT HOLT, M.D. AND HELEN L. FALES
NEW YORK

One of the conclusions reached as a result of the extensive study of calcium metabolism made in this laboratory [1] was that young children have the best absorption of calcium when their intake of fat is at least 3.0 gm. for each kilogram, and when the amount of calcium in the diet is in the proportion of 0.03 to 0.05 gm. of calcium oxid for each gram of fat. In a recent article on the fat requirement of children,[2] we have referred again to the importance of this ratio between the fat intake and the calcium metabolism. In an attempt to establish definitely the relation of the fat intake to the calcium absorption, we have recently carried out a series of metabolism experiments on normal children.

Seven healthy children, between 2 and 6 years of age, were observed. The calcium metabolism was determined while they were taking a modification of the usual house diet of the hospital, consisting of whole milk, cereal, bread with butter, meat or eggs, fresh vegetables, potato or rice and stewed fruit. After this preliminary observation, the fat was eliminated as far as practicable from the diet, the loss in calories being made up by an increase in carbohydrate. The total calories, the protein intake and the calcium intake were kept at about the same figure as in the preliminary period. This was accomplished mainly by substituting fat free milk for whole milk, increasing the bread, cereal and fruit, and adding cane sugar. These changes made it possible to give in place of a diet containing from 30 to 60 gm. of fat, one containing not more than from 5 to 8 gm. of fat daily, that amount being a component part of the bread, cereal, vegetables, etc. It is almost impossible to eliminate this small quantity of fat. After the children had been given this diet a week or more, the calcium metabolism was again determined. In two cases, it was possible to keep the child on the diet low in fat for several weeks and then to make another met-

---

* Received for publication, Jan. 18, 1923.

* From the Laboratories of the Rockefeller Institute for Medical Research and the Babies' Hospital.

[1] Holt, L. E.; Courtney, A. M., and Fales, H. L.: Calcium Metabolism of Infants and Young Children, and the Relation of Calcium to Fat Excretion in the Stools, Am. J. Dis. Child. **19**:201 (March) 1920.

[2] Holt, L. E., and Fales, H. L.: The Food Requirements of Children: III. The Fat Requirement, Am. J. Dis. Child. **23**:471 (June) 1922.

abolism observation. With four of the children, the usual amount of fat was afterward restored to the diet, and an additional control period studied.

The dietary changes made in these experiments are listed in Tables 1, 2, 3 and 4, which give the details of the diet of two of the children, both when they were taking the usual diet and when they were taking the low fat diet. The procedure used in these two cases was followed in the others, the only variations being in amounts. The diet in Cases 1 and 3 was like that in Case 2, that in Cases 4, 5 and 7, like that of Case 6.

The diet low in fat was undoubtedly also low in vitamin A, but in no case was the period during which this diet was taken long enough to cause the development of the symptoms usually accompanying a deficiency of vitamin A. The clinical effect of the reduced fat diet upon digestion was closely observed, and the influence upon the calcium metabolism was studied quantitatively. In some cases, the fat metabolism was also studied. In all instances, the metabolism period was of four days' duration.

TABLE 1.—Dietary Changes in Case 2, Period 1

Hour	Typical Mixed Diet
6 a.m.	8 oz. whole milk
10 a.m.	6 oz. cereal, 2 slices bread, with 2 level tsp. butter, 8 oz. milk
2 p.m.	1 egg or 1 oz. scraped beef, 4 oz. potato or rice, 2 oz. vegetable (spinach, carrots or string beans), 4 oz. prunes or apple sauce, 2 slices bread with 2½ tsp. butter, 8 oz. milk
6 p.m.	4 oz. cereal, 2 slices bread with 2 tsp. butter

Total calories, 1,930; calories per kilogram, 113; distribution of calories: fat, 31 per cent.; carbohydrate, 54 per cent., and protein, 15 per cent.; fat intake 65 gm., per kilogram 3.8; carbohydrate intake 254 gm., 14.8 per kilogram; protein intake 70 gm., 4.1 per kilogram

REPORT OF CASES

Case 1.—*Greatly reduced calcium absorption on low fat diet; absorption normal when fat was restored to the diet.* H. M., boy, aged 5 years, 6 months, whose digestion was normal, had been operated on two months previously for a brain cyst. Convalescence had been good. At the time of observation he was improving steadily and walking freely about the ward. He ate slowly but took all his food if given time. He was under observation for seventy-one days. During this period his weight fluctuated between 18.14 and 18.85 kilograms. There was a slow, but fairly steady, gain during the first six weeks, and after that a narrow fluctuation with slight decline. During a period of twenty-four days on the low fat diet the net weight change was from 18.1 to 18.4 kilograms, with a maximum of 18.5 four days before this diet was discontinued. At the beginning of the observation the child, then taking the usual mixed diet, was quite constipated, daily enemas being necessary to obtain any movement of the bowels. The stools were well digested and smooth, alkaline and not excessively hard. It seems probable that the constipation was mainly due to the lack of muscular activity.

The findings of a four-day preliminary metabolism period were obtained on a usual mixed diet (Table 5). The calcium metabolism was normal; that

TABLE 2.—Dietary Changes in Case 2, Period 2

Hour	Typical Low Fat Diet
6 a.m.	8 oz. fat free milk
10 a.m.	8 oz. cereal with 4 tsp. sugar, 2½ slices bread, 8 oz. fat free milk
2 p.m.	4 oz. potato, 2 oz. vegetable, 4 oz. rice with 2 tsp. sugar, 4 oz. prunes or apple sauce, 2 slices bread, 8 oz. fat free milk
6 a.m.	8 oz. cereal with 4 tsp. sugar, 2½ slices of bread, 8 oz. fat free milk

Total calories, 1,916; calories per kilogram, 104; distribution of calories: fat, 3 per cent.; carbohydrate, 81 per cent., and protein, 16 per cent.; fat intake 7 gm., 0.4 per kilogram; carbohydrate intake 378 gm., 20.6 per kilogram; protein intake 73 gm., 4.0 per kilogram

TABLE 3.—Dietary Changes in Case 6, Period 1

Hour	Typical Mixed Diet
6 a.m.	8 oz. milk
10 a.m.	4 oz. cereal with 1 tsp. sugar, 1½ slices bread with 1½ tsp. butter, 8 oz. milk
2 p.m.	1 egg or 2 oz. scraped beef, 4 oz. potato or rice with 2 oz. milk, 2 oz. vegetable (spinach, carrots or string beans), 4 oz. apple sauce or prunes, 1 slice bread, 1 tsp. butter, 6 oz. milk
6 p.m.	4 oz. cereal with 1 tsp. sugar, 1½ slices bread with 1½ tsp. butter, 8 oz. milk

Total calories, 1,635; calories per kilogram, 95; distribution of calories: fat, 34 per cent.; carbohydrate, 50 per cent., and protein, 16 per cent.; fat intake 61 gm., per kilogram 3.6; carbohydrate intake 198 gm., per kilogram 11.5; protein intake 63 gm., per kilogram 3.7

TABLE 4.—Dietary Changes in Case 6, Period 2

Hour	Typical Low Fat Diet
6 a.m.	8 oz. fat free milk
10 a.m.	6 oz. cereal with 2 tsp. sugar and 2 oz. fat free milk, 2 slices bread with 2 tsp. jam or jelly, 6 oz. fat free milk
12 m.	3 oz. orange juice
2 p.m.	2 oz. chicken (white meat) or 1 oz. very lean beef, 4 oz. potato with 1 oz. fat free milk, 2 oz. vegetable, 2 oz. rice with 1 tsp. sugar and 1 oz. fat free milk, 4 oz. prunes or apple sauce
4 p.m.	1 slice bread with 1 tsp. jam or jelly, 6 oz. fat free milk
6 p.m.	6 oz. cereal with 2 tsp. of sugar and 2 oz. fat free milk, 2 slices of bread with 2 tsp. jam, 6 oz. fat free milk

Total calories, 1,554; calories per kilogram, 80; distribution of calories: fat, 5 per cent.; carbohydrate, 77 per cent., and protein, 18 per cent.; fat intake 8.0 gm., 0.5 per kilogram; carbohydrate intake 292 gm., 16.8 per kilogram; protein intake 69 gm., 4.0 per kilogram

TABLE 5.—Calcium Metabolism in Case 1

	Period 1	Period 2	Period 3	Period 4
Diet	Regular mixed	Low fat	Low fat	Regular mixed
Length of time on diet	5 days	11 days	24 days	19 days
Weight change during period	+0.5 kg.	+0.27 kg.	—0.06 kg.	+0.05 kg.
Fat intake, gm. daily	38.0	5.0	5.0	50.0
Calcium oxid intake, gm. daily	1.89	1.89	1.89	1.67
Calcium oxid per gm. fat	0.049	0.380	0.380	0.033
Description of stool	Constipated, enema necessary	Normal, then acid and not well digested	Acid, foul, showing much fermentation	Normal
Total solids of stool, gm. daily	16.8	24.4	34.3	21.0
Total ash in stools	3.30	4.50	6.44	3.59
Calcium oxid per cent. of solids of stool	7.99	7.42	6.48	6.82
Calcium oxid excretion in feces, gm. daily	1.34	1.81	2.22	1.43
Calcium oxid absorption, gm. daily	0.51	0.09	— 0.33	0.24
Calcium oxid absorption per cent. of calcium oxid intake	27.5	4.8	0	14.3
Calcium oxid in urine, gm. daily	—	—	0.092	—
Calcium oxid retention, gm. daily	—	—	—0.422	—
Calcium oxid retention per cent. of calcium oxid intake	—	—	0	—

is, the absorption, 0.51 gm. daily, 0.028 for each kilogram, was very close to the average which we have found for healthy children of this age. The fat absorption, shown in Table 6, was normal, and the fat excretion in the stool about the usual amount, and in the usual distribution, as soap, free fatty acids and neutral fat. The fat intake was below that which we have considered desirable.

Most of the fat of the diet was then replaced by carbohydrate, the total daily amount of fat being reduced from 38 to 5 gm. The protein, calcium oxid and total calories remained practically the same as in the preceding period. The child took this food well. Coincident with the change in food a regular bowel habit was established, and the child had one stool a day without enema throughout the remainder of the period of observation. This change, however, could not be ascribed solely to the dietary change. The child was becoming increasingly active, had special care, and an effort was being made to train him to have a bowel movement every day. On this diet, however, the character of the stools gradually changed markedly. After about a week on the low fat diet the stools became large, mushy, acid and showed signs of fermentation. After three weeks the stools were very foul, and the acidity and evidences of fermentation were much more marked.

The calcium and fat metabolism were determined after one week and again after three weeks on the low fat diet. The findings of these periods are also shown in Tables 5 and 6. It is seen that after one week upon the low fat diet the total daily amount of solids in the stool had increased from 16.8 to 24.4 gm. and that the calcium oxid excretion had increased from 1.34 to 1.81 gm., causing the absorption to drop to 0.09 gm. or 0.005 for each kilogram. This absorption is insufficient to compensate for the normal loss which occurs in the urine (nearly 0.1 gm. daily). The daily fat excretion was 1.11 gm., giving an absorption of only 3.89 gm. of fat or 77.8 per cent. of the intake. The distribution of the fat in the stool was about normal. The decrease in the percentage absorption of fat when the intake was lowered confirms our previous observation that the excretion of fat tends to remain constant, and when the intake is low the percentage absorption is not so good as with a higher intake.

TABLE 6.—Fat Metabolism in Case 1

	Period 1	Period 2	Period 3	Period 4
Fat intake	38.0	5.0	5.0	50.0
Total fat in feces, gm. daily	1.33	1.11	0.98	1.78
Fat, per cent. of total solids	7.93	4.55	2.85	8.5
Soap, per cent. of total fat	42.0	39.0	23.0	36.0
Free fatty acids, per cent. of total fat	31.0	34.0	39.0	27.0
Neutral fat, per cent. of total fat	27.0	27.0	38.0	37.0
Fat absorption, gm. daily	36.67	3.89	4.02	48.2
Fat absorption, per cent. of intake	96.7	77.8	80.4	96.5

At the time of the second metabolism period on low fat diet the solids of the stools had more than doubled, averaging 34.3 gm. daily. The calcium excretion increased to 2.22 gm. daily—more than the intake—giving a negative balance of more than 0.1 gm. The daily calcium oxid excretion in the urine was 0.092 gm. Accordingly, the child had at this time a negative balance of calcium oxid of 0.422 gm. daily. The fat metabolism was similar to that in the preceding period.

The child was then put on the usual house diet, receiving 50 gm. of fat daily. After nineteen days, the metabolism of fat and calcium was again determined. The findings are included in Tables 5 and 6. The solids of the stool were 21.1 gm. daily, about the normal amount for a child of that age.

The calcium excretion was only 1.43 gm., giving an absorption of 0.25 gm. daily. The fat absorption was normal, 48.2 gm., that is, 96.5 per cent. of the intake.

This child had normal absorption of calcium oxid on a diet containing the usual amount of fat, the stools being normal. After the fat had been replaced by carbohydrate for one week, the stools became acid and showed excessive fermentation; the total solids were markedly increased; the calcium absorption dropped to a very low point. An additional two weeks on this diet emphasized the metabolism changes. The stools were much more acid and fermented, and the calcium absorption was negative. After the usual amount of fat had been restored to the diet, the metabolism of calcium oxid again became normal.

CASE 2.—*Greatly reduced calcium absorption on low fat diet, causing a negative balance.* G. L., a boy, aged 5 years, 10 months, was rather delicate and neurotic. The tonsils and adenoids had been removed at the hospital one week before the observation period. The child was under observation nineteen days, during which time there was a steady gain in weight from 16.7 to 18.1 kilograms. The child took eagerly all food offered and would have eaten more, although he was receiving 113 calories for each kilogram of body weight, which seemed generous for a child with the limited activity of a hospital patient. The bowel habit was regular, consisting of one or two stools daily. When on the usual diet the stools were formed, smooth and well digested. After twelve days on a low fat diet the stools became foul and acid and showed signs of excessive fermentation and much undigested food. The findings of the first metabolism period on the usual diet are shown in Tables 7 and 8. The absorption of calcium oxid and fat was excellent, the values being about normal. It is interesting to note that this child was receiving 65 gm. of fat daily and absorbing 94.3 per cent. of it.

TABLE 7.—CALCIUM METABOLISM IN CASE 2

	Period 1	Period 2
Diet	Regular mixed	Low fat
Length of time on diet	8 days	11 days
Weight change during period	+0.26 kg.	+0.10 kg.
Fat intake, gm. daily	65.0	7.0
Calcium oxid intake, gm. daily	1.93	1.95
Calcium oxid per gm. fat	0.030	0.280
Description of stools	Part normal, part soft and acid	Acid, much fermentation, undigested food residue
Total solids of feces, gm. daily	19.5	21.1
Total ash of feces, gm. daily	3.60	4.57
Calcium oxid per cent. of solids of feces	7.19	9.10
Calcium oxid excretion of feces, gm. daily	1.40	1.92
Calcium oxid, gm. daily	0.53	0.03
Calcium oxid absorption per cent. of calcium oxid intake	27.5	1.54

TABLE 8.—FAT METABOLISM IN CASE 2

	Period 1	Period 2
Fat intake	65.0	7.0
Total fat in feces	3.83	2.22
Fat, per cent. of total solids	19.67	10.50
Soap, per cent. of total fat	40.3	42.3
Free fatty acids, per cent. of total fat	32.4	25.1
Neutral fat, per cent. of total fat	27.3	32.7
Fat absorption, grams daily	61.2	4.79
Fat absorption, per cent. of intake	94.3	68.4

After nine days on a diet low in fat, but having the same caloric value and with the same protein and calcium oxid intake, another metabolism determination was made (Tables 7 and 8). The total solids of the stool had increased slightly, from 19.5 to 21.1 gm. daily. The calcium oxid excretion had increased from 1.4 to 1.92 gm., changing the absorption from 0.53 gm. daily to 0.03 gm. daily, which is less than the normal urinary excretion, that is, a negative balance was produced.

CASE 3.—*Calcium absorption apparently not influenced by a reduction of fat in the diet.* S. S., girl, aged 2 years, 9 months; normal, but not robust, was under observation for forty-five days. There was a steady gain in weight for twenty-eight days, then fluctuation without net loss for the remainder of the period of observation. The bowel habit was regular, but the stools were not often normal, being usually acid and showing excessive fermentation. This condition was much more marked when the child was put on a low fat diet. The stools became very acid and loose and contained much undigested food. During the time on the low fat diet the child vomited on three different days.

TABLE 9.—CALCIUM METABOLISM IN CASE 3

	Period 1	Period 2
Diet	Regular mixed	Low fat
Length of time on diet	14 days	17 days
Weight change during period	+0.07 kg.	+0.07 kg.
Fat intake, gm. daily	49.0	5.0
Calcium oxid intake, gm. daily	1.65	1.65
Calcium oxid per gm. fat	0.034	0.330
Description of stools	Part normal, part acid and undigested	Fermentation marked, acid undigested
Total solids of feces, gm. daily	14.8	17.8
Total ash of feces, gm. daily	2.03	3.73
Calcium oxid per cent. of solids of feces	7.54	5.59
Calcium oxid excretion in feces, gm. daily	1.11	0.99
Calcium oxid absorption, gm. daily	0.55	0.66
Calcium oxid absorption, per cent. of calcium oxid intake	33.2	40.0

TABLE 10.—FAT METABOLISM IN CASE 3

	Period 1	Period 2
Fat intake	49.0	5.0
Total fat in feces	1.74	0.98
Fat, per cent. of total solids	11.8	5.5
Soap, per cent. of total fat	9.6	31.9
Free fatty acid, per cent. of total fat	42.3	31.5
Neutral fat, per cent. of total fat	48.1	36.6
Fat absorption, gm. daily	47.3	4.0
Fat absorption per cent. of intake	96.5	80.4

Two metabolism periods were obtained, the findings of which are given in Tables 9 and 10. The fat and calcium absorption was excellent. The abnormal appearance of the stools was substantiated by the fat analysis. The proportion of soap was very much lower than is usual in normal stools, and the proportion of both free fatty acids and soap, very much higher than is normal. We have always found that such a distribution of the fat of the stool is an indication of a slight or impending digestive disturbance. With this child the calcium absorption was good, in fact a little better, on the low fat diet than on the usual diet. Although the total solids and also the total ash of the stool were increased, the calcium oxid excretion was less than on the usual diet. As the child was then removed from the hospital, further observations were not possible.

CASE 4.—*Calcium absorption apparently not influenced by a reduction of fat in the diet.* N. R., girl, aged 5 years, 6 months, was normal but rather delicate, being subject to minor digestive disturbances, particularly vomiting attacks. The tonsils were much enlarged. This child was under observation for thirty-six days. During the first seventeen days, while she was taking the usual diet, there was a steady gain in weight, the increase in that time being from 18.1 to 18.7 kilograms. During this time the first metabolism period was obtained. On the seventeenth day of observation the child had a digestive upset, vomited several times and refused much of her food. This condition persisted about three days. She was, nevertheless, put upon the low fat diet and took all the food well, although she vomited once on the second day. During the time on low fat diet there was fluctuation in weight, with a net loss of 100 gm. The child took all the food except during the digestive disturbance mentioned. She was receiving 1,662 calories daily, 103 for each kilogram. The bowel habit was regular throughout the entire time of observation, the child having one or two bowel movements daily. The stools were never entirely normal. They were rather undigested, showed signs of fermentation and were frequently acid. This characteristic was more marked on the low fat diet, the stools being then very acid and foul and showing marked fermentation.

TABLE 11.—Calcium Metabolism in Case 4

	Period 1	Period 2
Diet	Regular mixed	Low fat
Length of time on diet	10 days	13 days
Weight change during period	+0.28 kg.	—0.015 kg.
Fat intake, gm. daily	64.0	8.0
Calcium oxid intake, gm. daily	1.895	1.875
Calcium oxid per gm. fat	0.030	0.234
Description of stools	Part normal, part mushy, fermentation marked, acid	Marked fermentation, mushy, acid, very foul
Total solids of feces, gm. daily	23.73	27.00
Total ash of feces, gm. daily	4.65	4.32
Calcium oxid per cent. of solids of feces	6.54	5.19
Calcium oxid excretion in feces, gm. daily	1.550	1.401
Calcium oxid absorption, gm. daily	0.345	0.474
Calcium oxid absorption, per cent. of calcium oxid intake	18.2	25.2
Calcium oxid in urine, gm. daily	0.152	0.058
Calcium oxid retention, gm. daily	0.193	0.416
Calcium oxid retention, per cent. of calcium oxid intake	10.2	22.2

The findings of the metabolism determination on regular diet are shown in Table 11. The calcium absorption was good. The amount of solids in the stool was more than is normal for a child of this age. The findings for the observations on a low fat diet are also shown in Table 11. The solids were somewhat increased; but the calcium excretion, both in the stools and in the urine, was less than in the preceding period. Consequently, the child showed a much better calcium oxid retention in the low fat period. The child went home before further study was possible.

Case 5.—*Negative calcium balance on the low fat diet; normal absorption when fat was restored to the diet.* M. B., girl, aged 5 years and 7 months, was a large well-nourished child with normal nutrition. The Pirquet reaction was positive, but there was no clinical evidence of tuberculosis. She was under observation for fifty-six days. During this time, she gained weight steadily, the weight increasing from 19.9 to 21.3 kilograms. The weight gain was equally good on the regular diet and on the low fat diet, which was taken for twenty-eight days. The child was receiving about 82 calories for each kilogram of body weight. The appetite was always good, and the bowel habit was regular. The stools were normal, smooth and well digested on the usual diet; on the low fat diet they were usually mushy, acid and contained undigested food, though occasionally they were quite normal.

The findings for the metabolism periods are shown in Table 12. The calcium absorption on the regular diet was excellent. The total solids of the stools were increased, and the calcium oxid excretion in the stool was greatly increased, giving a negative balance of calcium oxid. The findings of a second observation on a low fat diet are shown in Table 12. During this period the amount of solids of the stools was not so high, about that of the first period, but the calcium oxid excretion was much higher than in the control period, producing a low absorption and retention, although better than in the preceding period on the low fat diet. The child was put again on the usual diet, and another observation was made, the findings of which are also shown in Table 12. The solids had dropped to a much lower figure; the calcium oxid excretion was low, and the calcium oxid absorption excellent.

Case 6.—*Greatly reduced calcium absorption on low fat diet, becoming normal when fat was restored to the diet.* G. S., boy, aged 6 years, was undernourished and rather delicate. The cervical glands and tonsils were markedly enlarged. Before admission the child had been fed very badly, receiving a great deal of candy, pastry and bread, and very little milk or meat. The child was under observation thirty-six days, during which time the general condition improved steadily with continuous gain in weight from 16.3 to 17.4 kilograms. He took about 95 calories per kilogram. The appetite was excellent and the bowel habit regular. The stools on the usual diet were smooth, well digested, occasionally mushy and showed some signs of fermentation. On the low-fat diet they were acid, foul and showed excessive fermentation. After the observation was completed, the child's tonsils and adenoids were removed, and nine days later another metabolism observation was made, the usual diet being taken. The stools at this time were normal. The findings for this child are shown in Table 13. The calcium oxid absorption was excellent on the usual diet. On the low fat diet the solids of the stool were increased somewhat; the calcium oxid excretion was increased, and the retention lowered to about one fourth of that in the preceding period. The results of the period after tonsillectomy show a low total solid content in the stool, a very low calcium oxid excretion and a high calcium absorption.

TABLE 12.—Calcium Metabolism in Case 5

	Period 1	Period 2	Period 3	Period 4
Diet	Regular mixed	Low fat	Low fat	Regular mixed
Length of time on diet	14 days	22 days	27 days	16 days
Weight change during period	+0.2 kg.	+0.05 kg.	+0.025 kg.	+0.035 kg.
Fat intake, gm. daily	64.0	8.0	8.0	64.0
Calcium oxid intake, gm. daily	1.895	1.875	1.875	1.895
Calcium oxid per gm. fat	0.030	0.234	0.234	0.030
Description of stools	Normal, smooth, well digested, alkaline	Part normal, mostly mushy, fermentation marked	Part normal, mostly mushy, fermentation marked	Normal
Total solids of feces, gm. daily	17.7	22.2	17.1	13.9
Total ash of feces, gm. daily	3.60	5.36	4.38	2.84
Calcium oxid per cent of solids of feces	8.42	9.42	10.14	8.01
Calcium oxid excretion in feces, gm. daily	1.490	1.995	1.735	1.110
Calcium oxid absorption, gm. daily	0.405	—0.120	0.140	0.765
Calcium oxid absorption, per cent. of calcium oxid intake	21.4	0	7.5	40.8
Calcium oxid in urine, gm. daily	0.054	—	0.031	—
Calcium oxid retention, gm. daily	0.351	—	0.109	—
Calcium oxid retention, per cent. of calcium oxid intake	18.5	—	5.8	—

Case 7.—*Greatly reduced calcium absorption on low-fat diet, becoming normal when the fat was restored.* J. K., boy, aged 2 years and 6 months, a normal child, fat and well nourished, was under observation for forty-seven days. The weight gain was continuous from 13.0 to 14.3 kilograms. The bowel habit was regular, and on the regular diet the stools were perfectly normal. On the low fat diet, the stools were soft and well digested, but foul and of a peculiar putty-like consistency. The metabolism findings are shown in Table 14. The calcium oxid absorption on the regular diet was excellent. On the low fat diet the calcium excretion in the stools was raised considerably, giving a lowered absorption of calcium oxid, and the excretion in the urine was also markedly increased, so that the retention was considerably less than on the usual diet, although still fairly good. After the regular diet was again given, observation was made for another period. The calcium excretion was very low, giving an excellent absorption of calcium oxid.

TABLE 13.—Calcium Metabolism in Case 6

	Period 1	Period 2	Period 3 *
Diet	Regular mixed	Low fat	Regular mixed
Length of time on diet	18 days	17 days	9 days
Weight change during period	0.11 kg.	0.055 kg.	0
Fat intake, gm. daily	61.0	8.0	64.0
Calcium oxid intake, gm. daily	1.895	1.875	1.895
Calcium oxid per gm. fat	0.031	0.234	0.030
Description of stools	Normal	Mushy, acid, foul	Normal
Total solids of feces, gm. daily	15.60	18.45	9.57
Total ash of feces, gm. daily	3.19	3.90	1.80
Calcium oxid per cent. of solids of feces	8.58	9.00	7.98
Calcium oxid excretion in feces, gm. daily	1.34	1.66	0.76
Calcium oxid absorption, gm. daily	0.555	0.215	1.129
Calcium oxid absorption, per cent. of calcium oxid intake	29.3	11.5	59.5
Calcium oxid in urine, gm. daily	0.083	0.079	—
Calcium oxid retention, gm. daily	0.472	0.136	—
Calcium oxid retention, per cent. of calcium oxid intake	24.9	7.3	—

* After tonsillectomy.

TABLE 14.—Calcium Metabolism in Case 7

	Period 1	Period 2	Period 3
Diet	Regular mixed	Low fat	Regular mixed
Length of time on diet	16 days	15 days	14 days
Weight change during period	+0.255 kg.	+0.02 kg.	—0.085 kg.
Fat intake, gm. daily	64.0	8.0	64.0
Calcium oxid intake, gm. daily	1.895	1.875	1.895
Calcium oxid per gm. fat	0.030	0.234	0.30
Description of stools	Ideally normal, smooth well digested, soft, formed, alkaline	Smooth, well digested but with peculiar putty-like consistency, very foul	Normal, but still putty-like
Total solids of feces, gm. daily	13.24	12.15	9.45
Total ash of feces, gm. daily	2.63	3.20	2.02
Calcium oxid per cent. of solids of feces	7.89	10.59	7.82
Calcium oxid excretion in feces, gm. daily	1.038	1.290	0.740
Calcium oxid absorption, gm. daily	0.767	0.585	1.131
Calcium oxid absorption per cent. of calcium oxid intake	40.5	31.6	60.4
Calcium oxid in urine, gm. daily	0.054	0.102	—
Calcium oxid retention, gm. daily	0.713	0.483	—
Calcium oxid retention, per cent. of calcium oxid intake	37.6	25.7	—

SUMMARY

1. A marked reduction of fat in the diet of the children studied uniformly changed the character of their stools from smooth, normal, alkaline and well digested, to acid and foul, with an excess of fermentation and undigested food residues. Whether this change was due to the reduction of the fat or the increase of carbohydrate, or to both factors, it is impossible to say definitely.

2. In five of the seven cases the calcium absorption was markedly reduced when the low fat diet was taken, in three cases a negative balance being produced. In the other two cases, the stools were never entirely normal, even during the control period, and the absorption was not lower on the low fat diet than it was on the control diet. These two children were very much alike so far as digestion and general symptoms were concerned. The chemical findings in the two cases were almost identical. It is impossible to offer any explanation of the differences between the results in these two cases and those obtained in the other five.

3. The increase of calcium oxid excretion was, in most instances, due partly to the fact that on the low fat diet the daily amount of total solids in the stool was markedly increased, and partly to the fact that the calcium oxid percentage of total solids of the stool was higher. In all but one case the total solids of the stool were increased on a low fat diet. In four cases the calcium oxid percentage of solids was increased. In all cases except one the total ash in the stool was higher on the low fat diet.

4. Although the results of these observations are not entirely uniform, the indications are that a low fat diet greatly diminishes calcium oxid absorption. Whether the absorption of calcium oxid is dependent on a definite relation between the fat and calcium in the diet, or whether the fat intake influences the calcium oxid absorption chiefly by the maintenance of proper digestive conditions, it is impossible to say. It is quite certain that a very low fat intake brings about abnormal digestive conditions, as judged by the type of stool. Finally, it seems safe to conclude that the conditions for proper calcium absorption are much better when the fat intake is generous.

American Journal of Diseases of Children

Vol. 25 APRIL, 1923 No. 4

BRAIN TUMORS IN YOUNG CHILDREN

A CLINICAL AND PATHOLOGIC STUDY *

MARTHA WOLLSTEIN, M.D.
AND
FREDERIC H. BARTLETT, M.D.
NEW YORK

Among 4,563 necropsy records at the Babies' Hospital, there are listed nine cases of neoplasm of the brain. While it is true that the brains of all these infants were not examined, because permission was not obtained, there is no instance in which there was a failure to examine the brain when a neoplasm had been suspected. This makes an incidence of 0.2 per cent., which is less than the 1 per cent. recorded for the occurrence of brain tumors among adults. There were two girls and seven boys, and their ages ranged from 2 weeks to 3 years.

The results of a study of seven of the cases are recorded in this paper. Five neoplasms were located in the cerebellum, constituting infratentorial tumors, and two in the cerebrum, constituting supratentorial tumors.

CEREBELLAR (INFRATENTORIAL) TUMORS

All five infratentorial tumors involved the vermis and extended into one lobe of the cerebellum, compressing the other lobe; all had distorted the medulla; three (Cases 1, 5 and 7) had compressed the upper cervical segment of the spinal cord; one (Case 2) had compressed the pons as well as the medulla; one neoplasm (Case 5) had extended into the pons and was accompanied by a cyst in the fourth ventricle (Dr. J. R. Hunt[1]), and another (Case 4) involved one of the cerebellopontile peduncles. None gave rise to metastasis in the other organs.

The tumors were all large, measuring from 4 by 3.5 to 9 by 10 cm. in diameter. They were situated under the pia, which was deep red or reddish blue over the growth. They were very vascular, containing small hemorrhages and areas of necrosis. One (Case 2) contained a small cyst as a result of softening.

Hydrocephalus was associated with all five tumors, but it was not excessive in any case. In only one instance (Case 1) were the cerebral

---

* Received for publication, Feb. 20, 1923.

* From the Babies' Hospital.

[1] Hunt, J. R.: Am. J. M. Sc. **127**:504, 1904.

convolutions flattened and the cerebral cortex thinned. In the other four, the cortical substance of the cerebral hemispheres was not thinner than normal, and the ventricular distention was moderate in amount. The hydrocephalus resulted from the closure of the foramen of Magendie by pressure of the tumor on the roof of the fourth ventricle. The meninges were never the seat of neoplasmic infiltration.

Histologically, these five infratentorial neoplasms were gliomas of the astrocytoma type.

These gliomas apparently began in the inferior vermiform process and extended anteriorly, upward and laterally, but more to one side than to the other; that is, both cerebellar lobes were not equally involved. Usually one lobe was infiltrated by the growth and the other was only compressed. Anteriorly, the tumors advanced to the anterior surface of the cerebellum and thus to the roof of the fourth ventricle; upward they spread to the middle cerebellar peduncles or to the pons. As a result of the direction of growth, the tumors under consideration pressed on the uninvolved portion of the cerebellar hemispheres and peduncles, on the pons, medulla and first cervical segment of the spinal cord. Secondarily, ventricular distention exerted pressure on the cerebral hemispheres, already compressed by the increased intracranial pressure resulting from the mechanical presence of the tumor. The cranial nerves were distorted and compressed as a result of pressure exerted by the tumor on the pons and medulla.

CEREBRAL (SUPRATENTORIAL) TUMORS

The two supratentorial growths were dissimilar in location and in structure.

One (Case 3) involved the following basal ganglions: the corpora striata and optic thalami, and the corpora quadrigemina. The left corpus striatum and the left optic thalamus were larger than the corresponding ganglions on the right. In this case the hydrocephalus was extreme, resulting in a compression of the cerebral cortex to a diameter of 3 mm. over several gyri in both hemispheres. The pressure of the growth on the third ventricle and on the foramina of Monro caused this distention of the lateral ventricles. The aqueduct and the fourth ventricle were not enlarged. A curious phenomenon in this case was the presence of an enormously dilated cisterna magna, making a bag of fluid, 4 cm. in diameter, on the under surface of the cerebellum. This must have been due to the gradual accumulation (by secretion) of fluid in the fourth ventricle and its entrance into the cisterna through the open foramen of Magendie. It was prevented from entering the cerebral subarachnoid space because this space was obliterated by the pressure of the large cerebral hemispheres. Histologically this tumor was a glioma (astrocytoma).

The second cerebral or supratentorial growth (Case 6) occurred in such a young child that the probability of its congenital origin can scarcely be doubted. The points of interest in the case are these: the age of the infant; the rapid enlargement of the head; the cerebral hernia after spontaneous rupture of the scalp and membranous left frontal bone; the extensive involvement of the left cerebral hemisphere, so that the point of origin could not be definitely determined, and the fact that the cranial enlargement was due less to the hydrocephalus in the right hemisphere than to distention of the left cerebral hemisphere with new growth. Histologically this tumor was a glioma sarcomatoides (Borst) or gliosarcoma.

TABLE 1.—Findings in Seven Cases of Brain Tumor

Approximate Age of Child at Onset of First Symptom	First Symptoms to Appear (Parents' Statement)	Approximate Duration of Disease (Onset to Death) Months	Sex*	Location of Tumor	Remarks
Case 1 R. P. 22 mos.	Stumbling gait and drowsiness	7½	♂	Glioma of medulla, pons, and vermiform process of cerebellum	Fontanel closed on admission to the hospital; no change in fontanel before death
Case 2 A. S. 35½ mos.	Vomiting	2½	♂	Glioma of cerebellum	Fontanel closed on admission to hospital; fontanel open before death
Case 3 F. D. 16¾ mos.	Paralysis of right arm and right leg	13	♂	Glioma of optic thalamus and corpus striatum	Fontanel closed on admission to hospital; fontanel open before death
Case 4 R. D. 12 mos.	Hydrocephalus	4	♂	Glioma of cerebellum	Fontanel open on admission to hospital
Case 5 W. J. 8 mos.	Vomiting	5½	♂	Glioma of cerebellum and medulla	Fontanel closed on admission to hospital; no change in fontanel before death
Case 6 S. K. 2 wks.	Hydrocephalus	1½	♂	Glioma-sarcomatodes of left cerebral hemisphere, probably beginning in left frontal lobe	Fontanel open on admission to hospital
Case 7 R. S. 9 mos.	Vomiting	1¼	♀	Glioma of the cerebellum	Fontanel open on admission to hospital
Average 15 mos.		Average 5 mos.	6 male 1 female		

* In this column, ♂ represents male and ♀ female.

Only one of the seven children presented a malformation in another organ than the brain. In Case 3, in which the boy had a glioma which involved the basal ganglions, there was also a horse-shoe kidney.

The average age of the children reported in this paper is about 15 months (Table 1). This places the time of the appearance of the tumors in this series of cases in the period of infancy. It is disconcerting to the clinician to discover at necropsy that puzzling symptoms shown by active infants have been due to the presence of tumor growth. There are certain conditions in infancy that may, in part, account for the delay in the appearance of symptoms resulting from the presence of a tumor in the brain. Infancy is the period of rapid growth and of adjustment to new environment. In this respect the infant differs from the adult. It must be remembered that the skull of a growing infant is distensible. Therefore, a growing brain and a distensible skull present two conditions which may delay the manifestations of a tumor growing in an infant's brain. From these statements it may be seen that in infancy one is confronted by a physiologic condition (a growing brain) and a mechanical condition (a distensible skull).

Infancy also presents a difficult problem resulting from the fact that an infant cannot give information about his own feelings. Even children of 2 or 3 years of age (Cases 1 and 2) are too young to report accurately subjective feelings. The first knowledge that there is anything wrong with a child comes from the observations of the parents or attendant. An adult will indicate that there is something wrong with him by declaring that he has a persistent headache, or that he feels nauseated, or that he has a dizzy sensation, or an unusual sensation in some part of his body. The evidence which an adult will give to a physician of such a disturbance an infant does not give. The result of this is that a new growth in the brain may reach a considerable size before it gives symptoms to which one's attention is directed. In other words the help given by subjective symptomatology is lacking in infancy.

Objective information derived from tests for disturbance of sensation are particularly inapplicable to children of the age reported in this paper, i. e., about 15 months. One is confronted, then, by this twofold problem in the interpretation of brain tumors in infants: First, a child has a new growth in the brain; it is not of an age to complain of its subjective feelings nor able to give early information that something is wrong; secondly, because of its age there is a physiologic condition (a growing brain) as well as a mechanical condition (distensible skull) which may delay the appearance of objective evidence which is so essential as a starting point for searching out the cause of any abnormal disturbance.

Early objective information given by motor disturbances apparently appears at a time when the tumor has grown to a considerable size. In the case of cerebellar tumors information derived from disturbance of gait is not available in young infants. The infants classified as Cases 3, 4 and 5 of this series were not yet walking. If an infant is learning to walk the superimposed stumbling gait from a cerebellar tumor would be difficult to differentiate from his learning-to-walk gait.

The earliest symptoms of brain tumor are those reported by parents or nurses. A study of these early symptoms in connection with pathologic findings in the cases in this series shows that in all probability the tumors had grown to a considerable size before giving physical signs.

The first symptom in Case 2 which called attention to the fact that there was something wrong was internal strabismus of the right eye and headache. The cerebellar tumor (compare necropsy report of Case 2) had grown to such a large size that it had distorted the pontine-medullary border. This distortion had compressed the right sixth nerve, causing the internal strabismus. At this stage of its growth the tumor was probably inoperable, and it was only when the tumor had reached this inoperable size that unusual symptoms were noticed.

The first symptom noticed in Case 3 was paralysis of the right arm and right leg. In this infant the tumor, starting in the left optic thalamus and corpus striatum, had invaded the left internal capsule. This infiltration had interrupted the conduction from the arm and the leg centers giving, in the paralysis, the first evidence of intracranial disease. This information, however, came at a time when the tumor must have been of considerable size and when operation for its removal would, probably, not be possible.

The first symptom in Case 4 to attract the attention of the parents was an increase in the size of the head. This was first noticed when the child was about 12 months old. He was brought to the hospital at 16 months of age. The enlargement of the head at 12 months was the result of accumulation of fluid in the ventricles. The tumor in the cerebellum had grown sufficiently in size to cause pressure on the roof of the fourth ventricle and close the foramen of exit. This case illustrates again the difficulty of making an early discovery of a new growth in the brain, since apparently in many instances there are no symptoms to attract the attention of the parents in the early stages of the growth of the tumor. This infant was not walking nor standing, and the characteristic cerebellar symptoms were not applicable.

The first symptom in Case 5 to attract attention was vomiting. The infant began to vomit at about 8 months of age. He vomited about every other day for two or three weeks, and then the vomiting became more frequent, two or three times a day. There was nothing unusual in the character of the vomiting. It was not noticed to be forcible. Vomiting is such a common symptom of digestive trouble that it is not surprising that its association with brain tumor should be overlooked in an infant of 8 months of age. Indeed, there is no evidence that in this infant the vomiting was the result of intracranial trouble. At 11½ months of age drooping of the right eyelid was noticed. The time between the vomiting and the ptosis was about three and one-half months. When the child was brought to the hospital, at 13½ months, the parents asked that it be admitted because of failure to gain in weight. The vomiting and the ptosis had apparently not worried them. The time between the onset of the vomiting and the entrance to the hospital was about five and one-half months. The baby died the same day on which he was admitted.

The necropsy report shows that by the time the baby was admitted to the hospital the tumor was probably inoperable. It is doubtful even whether a physciian would have been led to investigate the presence of a brain tumor when the baby began to vomit at 8 months. Furthermore, there is no evidence to prove that the baby vomited at that time because it had a brain tumor. The first significant symptom was the ptosis of the right eyelid with retraction of the mouth, and the baby lived only a month and a half after this was noticed. In all probability by 11½ months the tumor was too large to be removed. There is every reason to believe that, in infants of this series, the brain tumor had grown to a considerable size before it gave symptoms that attracted attention.

Cases 1, 6 and 7 have not been referred to in this connection; they only furnish added information to substantiate the foregoing statement.

It is unnecessary to refer in detail to the symptoms of brain tumor, after the new growth has reached a size sufficient to cause physical signs that alarm the parents, in the infants reported in this paper. These symptoms are comparable to those in adults; for example, spasticities, increased reflexes, focal paralysis, etc. The nervous symptoms have been arranged in the approximate order of appearance following the case history. It may be of interest to call attention to the appearance and disappearance of reflexes which some of the cases show. This may possibly be explained by changes of the blood pressure in the brain or in the tumor itself, or by the occurrence of hemorrhages in the tumor resulting in variation in its size. Such changes in the size would account for pressure symptoms when the tumor is larger, and relief of such symptoms when the tumor is smaller.

Especial interest attaches to Case 6. This infant's head began to enlarge when it was 2 weeks old. The necropsy showed, four weeks later, that the enlargement of the head must have been due to the size of the growth in the left cerebral hemisphere and, secondly, but in a less degree, to the accumulation of fluid in the right lateral ventricle through pressure of the tumor on the third ventricle. Undoubtedly, the new growth was of congenital origin. According to Virchow[2] hyperplastic gliomas are occasionally congenital.

---

[2] Virchow, Rudolph: Die Krankhaften Geschwülste **2**:148, 1864-1865.

Two symptoms commonly associated with brain tumor are vomiting and convulsions. Vomiting occurred in three instances (Cases 2, 5 and 7) as an early symptom. The character of the vomiting was not described as projectile except in Case 6. Vomiting was of the kind commonly seen in cases of disturbed digestion. While the patients were under observation in the hospital, none presented unusual frequency of vomiting, nor was the vomiting of an explosive type.

Convulsions occurred in only one instance (Case 1) in this series. This child had a convulsion a few hours before death. As convulsions in brain tumor are frequently mentioned in textbooks on diseases of infants and children, it seems desirable to call attention to their nonoccurrence in the infants reported in this paper, whose average age was about 15 months.

TABLE 2.—Results of Examination of Spinal Fluids in Seven Cases

	Amount, C.c.	Appearance	Pressure	Cells	Globulin	Sugar
Case 1:						
10/ 4/14......	30	Clear	Increased	10 per c.c.	0	0
10/14/14......	..	Clear	Increased	—	—	—
12/ 8/14......	15	Clear	Normal	Normal number	0	—
3/11/15......	30	Clear	—	—	—	—
Case 2:						
7/ 7/15......	27	Clear	Increased	—	—	—
7/ 8/15......	7	Clear	No increase	96 (polymorphonuclears, 19%; lymphocytes, 81%)	—	—
7/13/15......	20	Clear	No increase	7 (polymorphonuclears, 0; lymphocytes, 100%)	+	—
7/20/15......	15	Clear	Increased	10 (lymphocytes, 100%)	+	—
7/23/15......	20	Clear	No increase	3 (lymphocytes, 100%)	0	+
7/29/15......	15	Clear	Increased	5	0	—
Case 3:						
12/19/16......	5	Clear	Increased	5	+	—
12/22/16......	5	Clear	No increase	Few scattered red cells	±	+
10/29/17......	15	Clear	No increase	9	—	0
10/30/17......	25	Clear	Slight	21 (lymphocytes, 100%)	+	0
11/ 2/17......	20	Clear	Slight	15	+	0
Case 4 (none)						
Case 5.........	15	Clear	—	Polymorphonuclears, 1; lymphocytes, 12		
Case 6:						
1/21/14......	—	Yellow	Increased	Polymorphonuclears, 63%; lymphocytes, 37%	—	+
Case 7:						
9/23/17......	—	Clear	Increased	24 (lymphocytes, 100%)	—	0
9/26/17......	—	Clear	—	90 (polymorphonuclears, 9%; lymphocytes, 91%)	—	+

Infrequency of vomiting and infrequency of convulsions in the infants of this series may be explained by the gradual increase in intracranial pressure and by the extreme adaptability of the young brain tissue to pressure gradually applied. Given this gradually increasing pressure in a space which is distensible, that is, in a partially opened cavity, the skull, it seems reasonable to assume that the effects of compression expressed by vomiting and convulsions are delayed.

The spinal fluids (Table 2) obtained on lumbar puncture in these seven cases varied in amounts from 5 to 30 c.c. The pressure was increased only when the infants were seen early (Case 1 and 3).

Later in the disease the pressure was not increased. The fluid was clear and colorless, except in one instance (Case 6), when it was yellow. The cells were increased in only one instance (Case 6). In the other six cases they varied in number between 5 and 24. Globulin was increased only in Case 6, in which the fluid was yellow and the cells were increased in number. The xanthochromia in the spinal fluid of this case resulted from the vascularity of the tumor and the trauma incident to the cerebral hernia.

Case 5 illustrates a confusion which might arise in determining localization of cerebral tumors. The neoplasm in this infant occupied the right cerebral hemisphere and the right cerebellopontile peduncle. It was so large that it disturbed the pons and medulla and pushed them against the border of the foramen magnum. The effect of this was to compress the trunk of the left facial nerve. This pressure would explain the left-sided facial paralysis which was noted on admission. Such paralysis would be explained by a tumor in the right cerebellar hemisphere.

REPORT OF CASES

Case 1.—*History.*—R. P., boy, aged 2 years, was admitted to the Babies' Hospital, Sept. 29, 1914, because of a stumbling gait. He was the only child. The parents were well. There was no history of tuberculosis or syphilis. The birth had been normal. He was nursed for fifteen months, and had received a mixed diet since. He had never been particularly vigorous, although he had had no acute illness. About two months previously it was first noticed that he could walk only a short distance without stumbling. This difficulty had steadily increased until at the time of admission he could only occasionally cross a room without falling. Listlessness and a desire to sleep a great deal of the time had been associated with the stumbling gait since its onset. The appetite had always been good. The stools were regular. There was no pain.

Physical Examination.—The child was a well nourished and well developed white boy. He did not look sick. The anterior fontanel was closed; and the sutures were ossified. The skull bones were firm. The pupils were equal and reacted to light. The tonsils were enlarged, and the adenoids hypertrophied. There was no rigidity of the neck. The knee-jerks were exaggerated. There was double ankle clonus. The gait resembled that of a drunken man. The child fell to one side as he walked. He lifted his feet high and swayed from side to side. The head measured 51 cm. (20⅛ inches); the chest, 51 cm. (20⅛ inches); the abdomen, 47 cm. (18½ inches), and the height was 89 cm. (35 inches).

Course in Hospital.—October 5, both disks were blurred and the margins were indistinct. There was double papillitis. The knee-jerks were not obtained; there was no ankle clonus.

October 10, the knee-jerks were present. The disposition was good, and the child was happy.

October 14, slight nausea was present, probably from the ingestion of potassium iodid (30 grains a day). He had a mania for chewing rubber. He had eaten the rubber of one percussion hammer and had gnawed the rubber of a stethoscope. He vomited five times between September 29 and October 14, when he went home.

October 14 to 17, the child was at home.

Second Admission.—October 17, he was readmitted because of diarrhea. There was no change in the nervous symptoms compared with October 14 except that double ankle clonus was obtained.

October 27, there was no vomiting. The disposition was good. There was slight incoordination of the right hand noticed for the first time. He could not stand without support, and he reeled to one side.

November 2, papillitis was increasing in both eyes.

November 7, knee-jerks were not obtained. There was no ankle clonus.

November 11, knee-jerks were present. There was no ankle clonus. A coarse tremor of the right hand was apparent when he reached for objects; there was incoordination of the right hand.

November 28, papillitis was increasing.

December 3, there was persistent drowsiness all day; it was difficult to arouse him. He wakened for a few minutes, said a few words, and went to sleep again. The pulse was irregular. He refused food.

December 7, right facial paralysis developed. There was internal strabismus in the left eye. He was stuporous most of the time. A cracked-pot sound was elicited over the cranium (demonstrated by Dr. J. Ramsey Hunt).

December 8, the anterior cervical glands were swollen and sensitive.

October 17 to December 8, he vomited ten times.

December 14, his mind was clear; he was bright and happy.

December 20, there was slight drooping of the right corner of the mouth, internal strabismus in the right eye, coarse tremor of the right arm and hand on attempt to grasp objects. The knee-jerks were sluggish.

December 26, knee-jerks were not obtained.

January 16, the temperature ranged between 102 and 104 F. from January 6 to January 16. owing to double purulent otitis media and bronchopneumonia The slight facial paralysis persisted; the knee-jerks were difficult to obtain. Double ankle clonus was marked.

January 18, the eyes were examined. The disks were pale; the outlines, very indistinct; the vessels, not enlarged, and there was beginning atrophy of the disks.

January 20, there was no suggestion of facial paralysis. He could not stand alone or walk. There was slight optic atrophy, no vomiting, no evidence of headache. The knee-jerks were hard to obtain.

February 7, he sat up in bed the greater part of the time, and was bright and happy. There was no evidence of facial paralysis.

February 17, he began to vomit. This was accounted for by potassium iodid, 12 grains a day which was being given. He seemed slightly stronger on his legs when supported.

February 20, he vomited two or three times a day. He seemed to feel bad and was contented to stay in bed. He coughed, and the entire left lower lobe was filled with fine crackling râles.

February 27: Vomiting was projectile February 26 for the first time. The child had failed rapidly; he looked pale, thin and unhappy. He was fretful and irritable. Ophthalmoscopic examination revealed cloudiness and blurring of the disks. The vessels were enlarged and tortuous. A decompression operation was performed with puncture of the corpus callosum.

February 28, he talked brightly and intelligently and wanted to sit up.

March 2, there was noticeable strabismus. There had been no vomiting for two days.

March 5, there was no vomiting. He was less drowsy and stuporous; he played with his toys and talked brightly. Strabismus was still quite marked; more so in the right eye. The right eye was wide open, and the left lid drooped. There was slight right facial paralysis.

March 9, he was apathetic and stuporous. He sat in a chair or in bed most of the time with his eyes half closed. He answered questions slowly as if he did not understand. Articulation was indistinct. Ptosis of the left lid was marked. He vomited yesterday for the first time since February 27. Papillitis had entirely disappeared in the right eye; nearly so in the left eye. There was moderate atrophy of both disks.

March 11, he had been markedly drowsy for two days. There was utter muscular relaxation at present. The knee-jerks were increased, more so than at any time since admission. Ankle clonus was quite marked.

March 12, 12:30 p. m., coma had been complete in the morning. A hernia about the size and shape of a peanut was present at the site of the head operation. The knee-jerks were exaggerated. There was marked ankle clonus. A convulsion occurred early in the morning, the first since admission. He refused food. At 2 p. m. a cyanotic attack occurred. Color gradually returned. The reflexes were gone. Respiration was slow and shallow, about 8 per minute. He died at 2:30 p. m.

Necropsy Findings.—March 13, 1915: The body was that of a small and fairly well nourished boy, aged 3½ years. The head was large and square. There was a healed round area near the median line, in the right parietal bone, from which a button had been trephined. When the calvarium was removed, adhesions were apparent around this spot, but there was no recent inflammatory exudate on the meninges. The superior longitudinal sinus was quite empty; the lateral sinuses contained fluid blood.

TABLE 3.—Results of Laboratory Examinations in Case 1

Spinal Fluid	Oct. 4, 1914	Oct. 14	Dec. 8	March 11, 1915
Amount	30 c.c.	—	15 c.c.	30 c.c.
Appearance	Clear	Clear	Clear	Clear
Pressure	Increased	Increased	Normal	—
Cells	10 per c.c.	—	Normal no.	—
Globulin	None	—	None	—
Fehling's test	Negative	—	—	—

Wassermann test, negative; Pirquet test, negative; Eye grounds: Oct. 5, 1914, both disks blurred and margins indistinct; double papillitis. Nov. 2, 1914, papillitis increasing. Jan. 16, 1915, disks pale, outlines very indistinct; beginning of atrophy of disks. Feb. 22, 1915, cloudiness and blurring of disks; vessels enlarged and tortuous. March 9, 1915, papillitis had entirely disappeared in right eye, nearly so in left; moderate atrophy of both disks.

Both cerebral hemispheres showed flattening of the convolutions. The lateral ventricles were very much dilated, contained 400 c.c. of clear fluid, and measured 14 by 8 cm. The optic tracts were flattened, as were also the olfactory nerves. The cerebellum appeared wider than normal, owing to the enlargement of the vermis, which was very firm in its posterior half, and gave evidence of fluctuation anteriorly. On section, this fluctuation was found to be due to the dilatation of the fourth ventricle, which measured 3.5 by 2 cm. The tumor was 4 cm. wide and equally long. It occupied the inferior vermiform process and the roof of the fourth ventricle, which, in consequence, was greatly thickened and distorted. The floor of the ventricle was infiltrated with gray, translucent, gliomatous material. The aqueduct of Sylvius and the third ventricle were dilated. The pons was larger than normal because the growth had extended into its lower portion.

The two cerebellar hemispheres were equally compressed by the neoplasm. In the median line the substance of the superior vermiform process was only 8 to 10 mm. in depth, and in this region the neoplasm could be raised or shelled from its bed over an area of about 2 cm. Beyond this, however, in the right cerebellar hemisphere the tumor was growing into the cerebellar substance and was not removable. The middle cerebellar peduncles were compressed but not infiltrated by the new growth. The upper segment of the cervical cord was compressed.

Anatomic Diagnosis: Subpial neoplasm of the cerebellum, involving the vermis, right cerebellar hemisphere, medulla and pons; compression of both cerebellar hemispheres, medulla and first cervical segment of the spinal cord; hydrocephalus; trephine wound in skull.

Microscopic Examination.—The cells composing the growth were rather small. They had a comparatively large nucleus, and protoplasmic processes or fibrils were demonstrable in many. The processes ramified between and to those of other cells and were more numerous in some fields than in others. There were spindle cells between the round ones. In some fields these were numerous and in other fields they were few. With the (immersion) high power, the round cells were found to be chiefly star shaped. Beyond the tumor, the cerebellar tissue was edematous.

Diagnosis: Glioma (astrocytoma).

Case 2.—A. S., boy, aged 3 years, was admitted to the Babies' Hospital, July 6, 1915, because of internal strabismus of the right eye, and headache of about two weeks' duration. The father and mother were both healthy. The baby had been breast fed and had thrived. He had whooping cough six weeks before admission. He had been constipated since birth. He had had nosebleed three weeks previously. The present illness had begun about two weeks before admission. He vomited once a day; the right eye turned in, and he had headache. He had been drowsy for one week, and this had been the more noticeable the last two days. The breathing had been irregular for the last three or four days. He had suffered from stiffness of the neck for one day.

Physical Examination.—He was well nourished and decidedly apathetic. He was irritable if disturbed; recognized his parents' voices, and called them by name. His expression was drowsy most of the time. The way in which he reached out his hands suggested a disturbance of vision. There was internal strabismus of the right eye and nystagmus of both eyes. The neck was slightly rigid. The reflexes were normal. No Kernig nor Babinski reflex was elicited. The eye grounds showed papillary congestion. The line of the disk was indistinct, and the vessels were somewhat tortuous. The head measured 53 cm. (21 inches); the chest, 55 cm. (21¾ inches). The height was 97 cm. (38¼ inches). The abdomen measured 48 cm. (19 inches).

Course in Hospital.—July 8, the apathy had disappeared to a great extent. The child was bright, talkative, observant, but still irritable. Impairment of vision was shown by his reaching out when he walked and by his running into objects. Knee-jerks could not be obtained on either side. There was paralysis of the external rectus of the left eye.

July 16, he had to be fed by gavage. He was drowsy and resented being disturbed. The Kernig sign was positive; Macewen's sign was present. The reflexes were still absent.

July 25, he took food better. Vomiting occurred once a day. He was still drowsy and spoke only when aroused. Speech was inarticulate.

July 29, drowsiness was slowly increasing. He vomited on an average of once a day. Macewen's sign was more pronounced. Respiration was slow, 13 per minute and irregular; the pulse was 120 and somewhat irregular.

August 7, the only significant change since the last note was that stupor was so great that he could not be roused.

August 14, he was in a comatose state all the time. He never spoke nor did he comprehend what was said to him.

August 22, he was fed by gavage. Paralysis of the left side of face had developed in the last three or four days; but he could close the left eye perfectly.

August 31, the circumference of the head was 54.5 cm., as compared with 53 cm. on admission. Dropped wrists had developed during the last few days, more marked on the right side. He retained an adequate amount of food by gavage, and was gaining in weight.

September 3, the condition showed a decided change for the worse. Breathing was noisy; there was a rattle in the throat and large, moist râles in the chest. Drooping of both lids had been present for some time; but today there was a pronounced drooping of the right upper lid. Respiration was regular in depth and rhythm, 25 per minute. He did not move the extremities.

September 5, respiration was slow, deep and regular. No convulsions occurred. Temperature was 104.5 F. It began to increase two days previously. He died this morning.

Necropsy Findings.—Sept. 4, 1915: The body was that of a moderately emaciated white boy. The head seemed too large for the body. There were no skin lesions. The scalp was normal. The sagittal and lambdoid sutures were open, leaving a line of membrane 2.5 mm. between the bones. The posterior fontanel measured 0.5 by 0.5 cm. The dura and pia were smooth and glistening, their vessels moderatelyy congested, and without evidence of inflammatory exudate or tubercles. The contour of the cerebral hemispheres was normal. Their anteroposterior diameter was 17 cm.

TABLE 4.—Laboratory Findings in Case 2

Blood Examination	Leukocytes	Polymorphonuclears, per Cent.	Lymphocytes, per Cent.	Basophils, per Cent.
7/ 7/15	17,000	49	51	...
7/ 8/15	18,000	60	40	...
7/ 9/15	26,000	67	32	1
7/10/15	14,000	81	19	...
7/11/15	13,000	76	24	...
7/12/15	12,000	79	20	1
	14,000	65	35	...

Spinal Fluid	7/7/15	7/8/15	7/13/15	7/20/15	7/23/15	7/29/15
Amount	27 c.c.	7 c.c.	20 c.c.	15 c.c.	20 c.c.	15 c.c.
Appearance	Clear	Clear	Clear	Clear	Clear	Clear
Pressure	Increased	No increase	No increase	Increased	No increase	Increased
Cells	—	96 (polymorphonuclears, 19%; lymphocytes, 81%)	7 (polymorphonuclears, 0; lymphocytes, 100%)	10 (lymphocytes, 100%)	3 (lymphocytes, 100%)	5
Globulin	—	—	+	+	0	0
Fehling's test	—	—	—	—	+	—

Wassermann test	July 15	July 20	July 22
Blood	0	—	0
Spinal fluid	0	0	—

When the brain was removed 250 c.c. of fluid ran out, at first clear, later blood-stained. The cerebellum was large and asymmetrical. It contained a firm, round neoplasm occupying part of the left hemisphere and all of the inferior vermiform process. The right cerebellar hemisphere was indented to receive the right border of the tumor, which contained a cyst, 1.5 cm. long anteroposteriorly. It was covered with a shell of cerebellar substance, 2.4 cm. thick, and could be shelled from its bed except on its superior surface where it infiltrated the cerebellum.

On section, the growth was pinkish gray, firm and vascular, with one necrotic zone, 0.5 cm. in diameter. This area of necrosis was yellow and had a small cavity in its center, evidently the result of a small hemorrhage. The medulla was distorted because the growth pushed it toward the right. Consequently, the left half of the medulla was narrower and thinner than the right half. The pons was less changed externally. The fourteenth ventricle was large, with its floor distorted from pressure of the tumor in the medulla. The aqueduct of Sylvius and the lateral ventricles were dilated. The cerebral substance was firm and only slightly thinner than normal. The optic tracts appeared to be atrophied.

Anatomic Diagnosis: Subpial neoplasm of the cerebellum, involving the left hemisphere and the vermis; hydrocephalus; compression of the right cerebellar hemisphere, pons and medulla.

Microscopic Examination.—The characteristic cell in the tumor had a round body with demonstrable processes. Very few spindle shaped cells were seen. Blood vessels were numerous in the network between the cells, and small hemorrhages were present. Through the soft, yellow part of the tumor, the section showed a blood clot surrounded by a zone of necrosis.

Diagnosis: Glioma (astrocytoma) of cerebellum.

Localization of the Tumor: Subpial neoplasm of the cerebellum, involving the left hemisphere and the vermis; compression of the right cerebellar hemisphere, pons and medulla; hydrocephalus.

Case 3.—F. D., boy, aged 17 months, was admitted to the Babies' Hospital, Dec. 18, 1916, because of paralysis of the right arm and leg. This condition was noticed about one week before. The parents were healthy; and there were two other healthy children. Birth had been normal. The baby was breast fed for four months and after that he was given milk formulas. He did fairly well, gained slowly, and weighed 16 pounds at 14 months of age. His development was that of a normal child. At 11 months he spoke single words. About one week previously, it was first noticed that he held his bottle with his left hand instead of with both hands. At the same time he did not move his right leg. With the appearance of the paralysis there was apparently no fever. For about one week he had been more drowsy and had slept more than usual. He had had a discharge from the left ear for about two months and from his right ear for about one week. There had been no convulsions, and no symptoms of disturbed digestion.

Physical Examination.—The baby was poorly nourished but did not look acutely ill. The edge of the liver was felt 2 cm. below the costal margin. The edge of the spleen was felt 2 cm. below the costal margin. There was no other variation from normal in the physical examination except in the nervous system. The head was not retracted. There was a slight stiffness of the neck on flexion of the head. The fontanel was closed. The face was drawn to the left. The eyes showed vertical and rotary nystagmus. The right eye was held partly open. Paralysis of the right arm was apparently complete. The legs were held rigid in extention. The left could be moved better than the right. At times the legs were crossed. He held his breath when he cried. The knee-jerks were active; the left more than the right. Patellar clonus was present on the right side. Ankle clonus was occasionally present on the left side. The Achilles reflex was active on the left side. The jaw reflex was hyperactive. Chvostek's sign was active. There was no carpopedal spasm. There was a slight Brudzinski sign.

Course in Hospital.—Dec. 23, 1916: The child was bright. He moved his head and tried to talk. Variability of physical signs was noticeable.

December 28, power in the right arm and leg had slightly returned. Paralysis of the right side of the face was sometimes pronounced; at times hardly noticeable. The child seemed much improved since admission.

Jan. 1, 1917, the weakness of the right side of the face and of the right arm and leg showed little change. At times it seemed less.

January 14, nutrition was slowly improving. There was no change in the nervous symptoms.

January 31, the most noticeable symptom for the previous two weeks had been irritability. This was particularly pronounced when the child was handled.

The condition was slowly becoming worse. He took his feedings fairly well. There was no special change in the weakness of the right arm and leg. At times it semed to be less and again the condition showed no change.

February 12, the child appeared better and brighter. The appetite was fairly good. Weakness of the right side was not so evident.

February 14, he had seemed better the preceding two days. He had gained considerably in weight. The weakness on the right side was not so evident. The appetite was improving. He was discharged to return for observation.

Discharge diagnosis was: marasmus, improved; infant feeding, improved; tetany improved.

Second Admission.—The baby was admitted to the hospital for the second time Oct. 29, 1917, when he was 2 years and 3 months old, because of a large head, a condition which was first noticed three months previously. The bowels had always been constipated. They moved once in three days and then only with castor oil. The child had to be forced to eat, and had taken only liquid food for several months.

Physical Examination.—He was poorly nourished, and the head was enormous. The baby lay in a position of opisthotonos and left pleurothotonos. The legs were rigid, and the legs and feet were extended. He was startled only by very loud noises. He was in a semicomatose state, sleeping most of the time. He did not sit up. He took no notice of his surroundings; he did not recognize his parents. He did not follow light, and apparently did not see. These symptoms had evidently been present for some time. The pupils reacted sluggishly. There was external strabismus in the right eye, and nystagmus of both eyes. The fundi showed double optic atrophy. The neck was rigid; flexion was almost impossible. Spasticity of all four extremities was noted, more pronounced on the right side. The fingers were flexed over adducted thumbs. The legs and feet were extended. There was wasting of the extremities. The palm muscles of the right hand and especially of the right thenar eminence were more atrophic than the left. The supinator reflex was exaggerated on both side. The triceps, biceps and knee reflexes were difficult to obtain on account of rigidity. The Achilles reflex was present and not exaggerated. The abdominal, epiglottic and cremasteric reflexes were not obtained. Ankle clonus was not obtained. The baby cried when pricked with a pin but did not attempt to draw its foot away. The head measured 55 cm. (21⅝ inches); the chest, 42 cm. (16⅝ inches). The height was 80 cm. (29¼ inches).

Provisional Diagnosis: Hydrocephalus, spastic quadriplegia, optic atrophy, idiocy, marasmus.

Course in Hospital.—October 30: The eye grounds were examined by Dr. Thomson. There was definite optic atrophy, more marked in the left eye. The atrophy was probably primary and of about one year's duration.

October 31, examination of the nervous system by Dr. Hunt revealed: hydrocephalus, probably secondary to some acute inflammatory process, as meningococcus infection, meningo-encephalitis or ependymitis causing a blocking of the aqueduct and of the foramina of Luschka.

November 5, cerebrospinal fluid leaked from the ventricular tap made October 31. The head was 54 cm. in circumference.

November 14, the head was 55.5 cm. in circumference. One cubic centimeter of phenolphthalein was injected into the right lateral ventricle. At lumbar puncture, twenty minutes later, 25 c.c. of clear spinal fluid was withdrawn. A faint trace of phenolphthalein appeared in Tube 2, which became definite in Tube 3. Twelve hours after injection of phenolphthalein it was still present in the spinal fluid.

November 20, lumbar puncture was performed, 60 c.c. of cerebrospinal fluid being withdrawn. No phenolphthalein was present. The head measured 57 cm. before puncture; 56.5 cm. after puncture. The child was steadily growing worse.

December 16, the circumference of head was 58 cm. He was semicomatose.

December 25, he was semicomatose; opisthotonos was marked; there was pleurothotonos to the left side. The sutures were wide open. The pupils were dilated, the right larger than the left. There was no reaction to light. Almost every forty-five seconds there were noted a rapid oscillation and lateral nystagmus, usually to the right. The neck was rigid and retracted. The heart was regular in rhythm. The fingers were reflexed over the thumbs and rigid. The arms were held rigid; more so on the right side. There was hyperextension at the right elbow joint; the forearm was flexed only with considerable force. Both upper arms were held close to the side, drawn in by contraction of the pectoral muscles. This was more pronounced on the left side. There was marked scissors deformity caused by adductor spasm between the knee and hip joints. It was impossible to flex the right knee joint. The toes of the right foot were in plantar flexion; the left in dorsal flexion. The muscles of the lower extremities were much wasted. The only movement in the lower extremities was at the hip, where there was a slight flexion. None of the deep or superficial reflexes were obtained. There was a growth of fine hair over the cheeks, abdominal wall (extending to the midclavicular line), thighs and both legs. The eyelashes measured at least 1 cm.

Jan. 6, 1918, the baby was growing weaker daily. For three days he had seemed moribund. Three large decubital ulcers had appeared over the occiput exposing the bone. The lower teeth were bent back so that they lay almost parallel with the floor of the mouth.

TABLE 5.—Laboratory Findings in Case 3

Spinal Fluid	12/19/16	12/22/16	10/29/17	10/30/17	11/2/17
Amount	5 c.c.	5 c.c.	15 c.c.	25 c.c.	20 c.c.
Appearance	Clear	Clear	Clear	Clear	Clear
Pressure	Increased	No increase	No increase	Slight	Slight
Cells	5	Few scattered red cells	9	21 (lymphocytes, 100%)	15
Globulin	+	Faint	—	—	—
Dextrose	+	+	—	—	—
Noguchi test	—	—	+	+	+
Fehling's test	—	—	0	0	0
Remarks	—	—	—	Right ventricle	Left ventricle

Wassermann test, blood and spinal fluid	Negative
Pirquet test	Negative
Urine	Negative
Eye grounds	Negative

January 15, he had grown progressively weaker since the last note. He had appeared moribund for days. He rarely cried when disturbed, and died quietly this morning.

Necropsy Findings.—Jan. 13, 1919: The body was that of a markedly emaciated, white boy with a large hydrocephalic head. All sutures were wide open. There were three large decubital ulcers over the occiput, exposing the skull; there was one smaller decubital ulcer over the sacrum.

After opening the cranium, 1,500 c.c. of fluid was withdrawn from the ventricles. The brain immediately collapsed. The surface of the brain was covered with dilated and congested vessels; but there was no evidence of inflammation of the meninges. The cerebral cortex was only from 3.5 mm. to 5 mm. thick. The thinnest portion was just in front of the left fissure of Rolando. At the base of the left cerebral hemisphere there was a tumor 7 by 6 cm., which involved both optic thalami and both corpora striata. The left ganglions were much larger than the right. The tumor was sharply separated from the pons. In the floor of the left lateral ventricle the tumor measured 8 by 9 cm. The right lateral ventricle was less dilated than the left, and its walls showed no bulging at any point. The aqueduct of Sylvius and the third ventricle were not dilated. The foramina of Monro were obliterated by direct pressure of the tumor. The choroid plexus in the floor of the lateral ventricles was much flattened. The cisterna magna was dilated to such an extent that it formed a cyst, 4 by 4 cm. Over the tumor the pia arachnoid was very thick and yellow. There were no signs of acute meningitis. The pons was asymmetrical because the neoplasm had pressed upon the anterior portion of its left half. The left cerebral peduncle was much compressed. The entire interpeduncular space was obliterated.

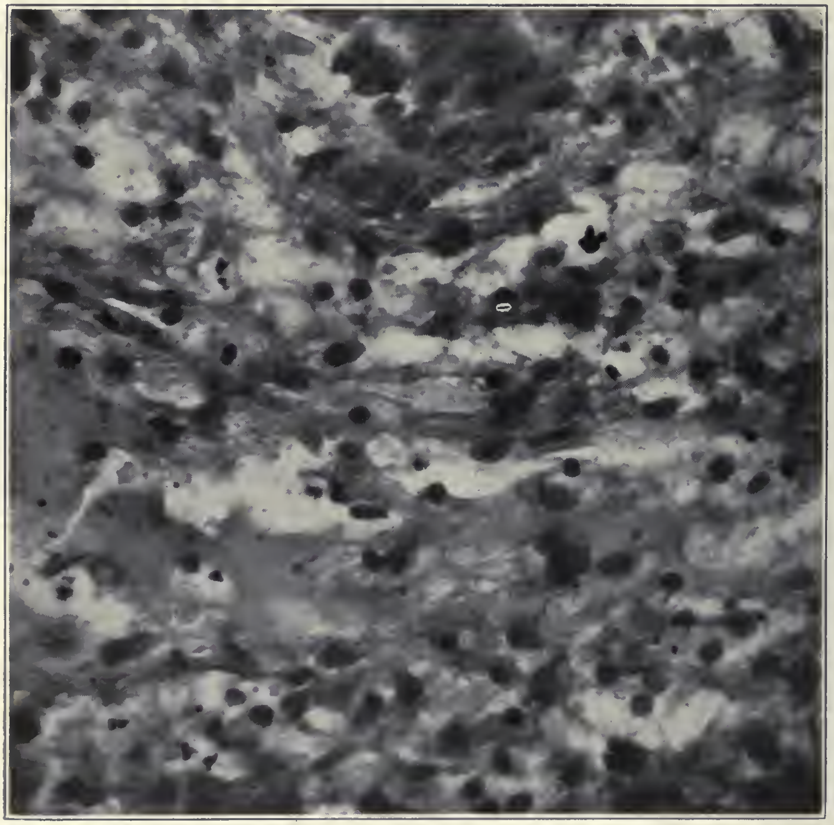


Fig. 1 (Case 3).—Glioma of the basal ganglions, marked edema; reduced from photomicrograph; × 250.

On section, the tumor was yellow, gelatinous in some portions, with areas of hemorrhage and softening. The posterior half was more firm in consistency.

The cerebellum was flattened from the weight of the enlarged cerebral hemispheres. The upper cord segment and the medulla were normal in outline.

Anatomic Diagnosis: Glioma of optic thalami and corpora striata (telencephalon and diencephalon); hydrocephalus; compression of cerebellum, pons and left cerebral peduncle.

Microscopic Examination of the Tumor.—There was marked edema, and some fairly large blood vessels contained thrombi. These were surrounded by areas of necrosis in which all cell structure had been lost. The cell unit was star-shaped, with a small round body and nucleus. The processes united to form a network. Blood vessels were numerous and had very thin walls. No spindle cells were present. There were large spaces filled with serum.

Diagnosis: Glioma (astrocytoma) of basal ganglions (Fig. 1).

Localization of the Tumor: Glioma of optic thalami and corpora striata (telencephalon and diencephalon); compression of the cerebellum, pons, left cerebral peduncle and optic tract; hydrocephalus.

Case 4.—R. D., boy, aged 16 months, was admitted to the Babies' Hospital, June 21, 1913, because of a large head. The increase in size was first noticed about four months previously. The parents were healthy. One other child had died during forceps delivery. The birth of this baby was normal. He had been breast fed. He sat alone at 10 months, and had just begun to walk and talk before this illness. He was always bright and playful. The head had begun to increase in size about four months before admission. There was no history of infection. He had never had convulsions.

Physical Examination.—The child was poorly developed, poorly nourished and apathetic. The expression of the face was dull and apathetic. Facial paralysis on the left side was complete. There was spasm of the muscles of the jaw. The mouth was opened with difficulty. The sagittal sutures were open, as was also the posterior fontanel. The anterior fontanel measured 11 by 7 cm. Expansion of the chest was less on the right side. This apparently was due to paralysis of the sternomastoid and scalenus muscles. The arms were held motionless, and both of them were rigid. The legs were both spastic. There was pronounced spasticity of the muscles about the foot and hip. The knee-jerks were both exaggerated, the left more than the right. The eye grounds were not examined because of a film which covered both. The child died six hours after admission. The head measured 56.5 cm. (22½ inches); the chest, 40 cm. (15¾ inches). The height was 75 cm. (29½ inches). The abdomen measured 34 cm. (13⅜ inches).

TABLE 6.—Laboratory Findings in Case 4

Spinal Fluid:	Amount	30 c.c.
	Appearance	Clear
	Pressure	Slightly increased
	Cells	5 per c.c.
	Globulin	+
	Film	None found
	Organisms	None found

Necropsy Findings.—June 23, 1913: The body was that of a fairly well developed and well nourished boy.

The head measured 22½ inches. The dura mater was congested, and there were adhesions between the dura and the pia, more numerous over the right hemisphere. At the base the dura mater was smooth. The pia was congested everywhere, and over the interpeduncular space it was thickened and turbid. There was no acute inflammatory exudate at any point.

The brain was very large, 700 c.c. of fluid came from the ventricles. The cerebellum, pons and medulla weighed 290 gm.; the cerebrum weighed 1,142 gm. The lateral ventricles were much dilated, but the cerebral substance was not greatly thinned. It measured 3 cm. in depth. The gray matter was pinker than normal; the white matter was unchanged in color. The consistency of the cerebral substance was normal. There was no tumor nodule in the cerebrum. The choroid plexuses were congested.

The cerebellum was much enlarged and measured 13 cm. transversely and 5 cm. anteroposteriorly. On the surface of the right cerebellar hemisphere, the pia mater appeared turbid, thickened and bluish. The two hemispheres were joined by a tumor mass, which obliterated the vallecula and extended into the right half of the cerebellum. On the upper surface of the cerebellum, the mass was also apparent, and its transverse diameter measured 4 cm. This mass was a round, deep red tumor, separated from the cerebellar substance by a compressed area of white matter limiting it as with a capsule over part of its circumference, but infiltrating the cerebellum over the rest of its extent. The tumor occupied the entire depth and length of the median line of the cerebellum. It was firm. Many blood vessels were apparent in its substance, but no hemorrhages had occurred. The tumor was more deeply red than was the cerebellum itself. The substance of the right cerebellar hemisphere measured only 1 cm. in thickness, while the left hemisphere was four times as thick. The widest part of the tumor measured 7 cm. The growth had extended into the right cerebellopontile peduncle, over an area 3 cm. in diameter and 2.5 in depth. Here the tumor was of the same color and consistency as the larger one. It was covered by a layer of white matter and distorted the medulla and the left peduncle. The medulla was pushed to the left, and the cranial nerves along its left border were pressed against the bone.

TABLE 7.—Laboratory Findings in Case 5

Spinal Fluid: Amount	15 c.c.
Appearance	Clear
Cells: polymorphonuclears	1
lymphocytes	12
Globulin	0
Sugar	0
Film	None formed
Wassermann test	Negative
Pus from right tonsil	No tubercle bacilli found
Pirquet test	Negative
Intradermal tuberculin test	Negative
Urine	No abnormal findings

The medulla contained no neoplasm. The growth seemed to be limited to the vermis, right cerebellar hemisphere and right middle peduncle.

Anatomic Diagnosis: Subpial neoplasm of the cerebellum, involving the vermis, right cerebellar hemisphere and right cerebellopontile peduncle; compression of medulla and left middle peduncle; hydrocephalus.

Diagnosis: Glioma (astrocytoma) of the cerebellopontile peduncle.

Localization of Tumor: Subpial neoplasm of the cerebellum, involving the vermis, right cerebellar hemisphere and right cerebellopontile peduncle; compression of medulla and left middle cerebellar peduncle; hydrocephalus.

Case 5.—W. J., boy, aged 13 months, was admitted to the Babies' Hospital, Sept. 30, 1921, because of failure to gain in weight for about five months. The parents were healthy. There was one other child, who was well. Birth had been normal. The patient had been a vigorous child up to 8 months of age, that is, until five months before admission. At 8 months he was sitting up alone and would stand holding onto a chair. He had frequent attacks of bronchitis. At 8 months of age (five months previously), he began to vomit the morning feeding. This had been repeated every second day. After two or three weeks he vomited two or three times a day, and, with the onset of vomiting, he began to lose weight. The bowels became constipated at the beginning of the illness. He weighed 26 pounds at 8 months of age. No other symptoms except vomiting and failure to gain in weight were noticed up to six weeks previous to admission, that is, when he was about 11½ months of age. At this time ptosis of the right eyelid and retraction of the mouth were noticed. The mental condition at 11½ months was bright.

Provisional Diagnosis: Feeding case, encephalitis.

Physical Examination.—The child was much emaciated. He lay flaccid in bed and paid no attention to his surroundings. Mucopurulent material escaped from the mouth and nostrils with each breath. The anterior fontanel was closed. The pupils were equal and reacted to light. There was ptosis of the right eyelid. Weakness of the entire left side of the face was noted. The mouth drooped to the left and was wide open on that side. From both nostrils mucopus was escaping. There was no rigidity of the neck, and no paralysis of the extremities. A good view of the soft palate was not obtained, but partial paralysis was probable because fluid given by mouth was returned through the nose. The abdominal reflexes were absent on the right side and present on the left side. The triceps reflexes were absent. Ankle clonus was not noted on the right; it was present on the left. There was no Kernig sign. Sensation was apparently undiminished.

Measurements: The height was 78.5 cm. (31 inches); the head measured 47 cm. (18½ inches); the chest 34.5 cm. (15½ inches); the abdomen 30.5 cm. (12 inches).

Diagnosis: Epidemic (lethargic) encephalitis; acute bronchitis.

Course in Hospital.—October 1, a more satisfactory examination of the pharynx revealed paralysis of the right side of the palate. Dr Johnson, who examined the child outside, stated that he saw pus escaping from behind the right tonsil.

October 4, neurologic examination by Dr. J. R. Hunt revealed that there was apparently a sympathetic ptosis of the right eye. There was slight rigidity of the neck and slight asymmetry of the facial innervation, on the right more than on the left. Otherwise, there were no objective symptoms referable to the nervous system. It is possible that the peritonsillar pressure was responsible for the sympathetic ptosis and mechanically caused asymmetry of the soft palate. (This observation was confirmed at necropsy.)

October 6, the eyes were examined by Dr. E. S. Thomson. The optic nerves showed no change; but the vessels, central artery and vein were somewhat dilated and rather active for general depression. The right third nerve showed some irritation in the pupillary and levator branches. The left facial nerve was partly paralyzed. There was nystagmus and probably a multiple intracranial lesion. The progressive downward course of this case led to the general belief that it was a case of brain tumor rather than encephalitis.

October 7, the child died.

Necropsy Findings.—Oct. 8, 1921: The body was that of an extremely emaciated, white male infant. The scalp and cranial vault were normal; the dura showed no lesion. Over the cortex, the pia was markedly edematous, and almost gelatinous in consistency. The vessels all contained easily movable thrombi. There was no evidence of cerebral hemorrhage, nor were sclerotic areas present. The frontal lobes appeared to be unusually short, especially on the upper surface. On removing the brain an increased amount of cerebrospinal fluid ran out. Over the inferior surface of the cerebrum the vessels of the pia were markedly less congested than over the cortex, and, in contrast, the inferior surface of the right cerebellar hemisphere appeared dark red. This was due to a subpial neoplasm, irregular in surface contour, and measuring 5 by 4 cm. in diameter. This growth occupied the anterior half of the right cerebellar hemisphere and encroached on the medulla and the vermiform, but not on the left cerebellar hemisphere (Fig. 2).

The medulla and the first cervical segment of the cord were pushed to the left, and the consistency of the medulla was very soft. The posterior border of the pons was also involved in the growth. There was no distinct line of demarcation between the neoplasm and the brain substance, and the growth could not be peeled out.

When transverse sections were made through the hemispheres after hardening, the lateral ventricles were found dilated to a moderate degree and equally.

The tumor occupied the anterior half of the right cerebellar hemisphere, and all of the vermiform process. It formed the roof of the fourth ventricle as well as its sides. The medulla was compressed from above downward and to the left. The cavity of the fourth ventricle was dilated; but it was largely filled by a cyst of irregular shape, which extended into the aqueduct of Sylvius above and into the substance of the cerebellar tumor behind (Dr. Hunt). This cyst caused the soft consistency of the medulla noted in the fresh specimen. The wall of the cyst was adherent to the floor of the fourth ventricle. The aqueduct of Sylvius was dilated (Fig. 3). The third ventricle and the foramina of Monro were also dilated.

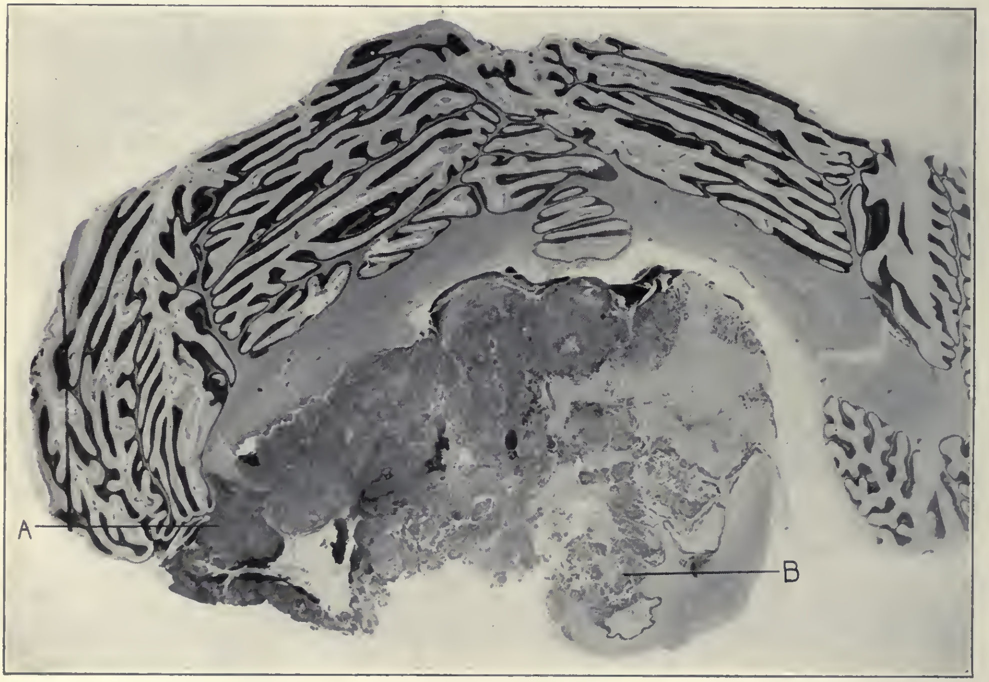


Fig. 2 (Case 5).—Glioma involving the right cerebellar hemisphere, vermis and medulla: *A,* glioma infiltrating the cerebellar substance; *B,* glioma infiltrating the medulla, which is pushed to the left.

Microscopic Examination.—The pia arachnoid was normal; its vessels contained blood. The nerve cells were in good condition, both in the anterior and in the posterior horns. In the posterior column there was a rarefied area about several blood vessels as though edema and slight loss of nerve elements had occurred.

The cells composing the new growth were round, with comparatively large nuclei. Many nuclei showed karyokinesis. Fusiform cells were not numerous, but processes could be demonstrated on the round cells. The blood vessels were very thin walled, small and numerous. The cerebellar substance just beyond the infiltrating neoplasm was edematous. In the aqueduct of Sylvius, a markedly edematous piece of the cyst wall was apparent. The substance of the pons was free from tumor growth.

Anatomic Diagnosis: Subpial neoplasm of the cerebellum, involving the right cerebellar hemisphere, vermis, medulla and pons; cyst of fourth ventricle; compression of the medulla and first cervical segment of the spinal cord.

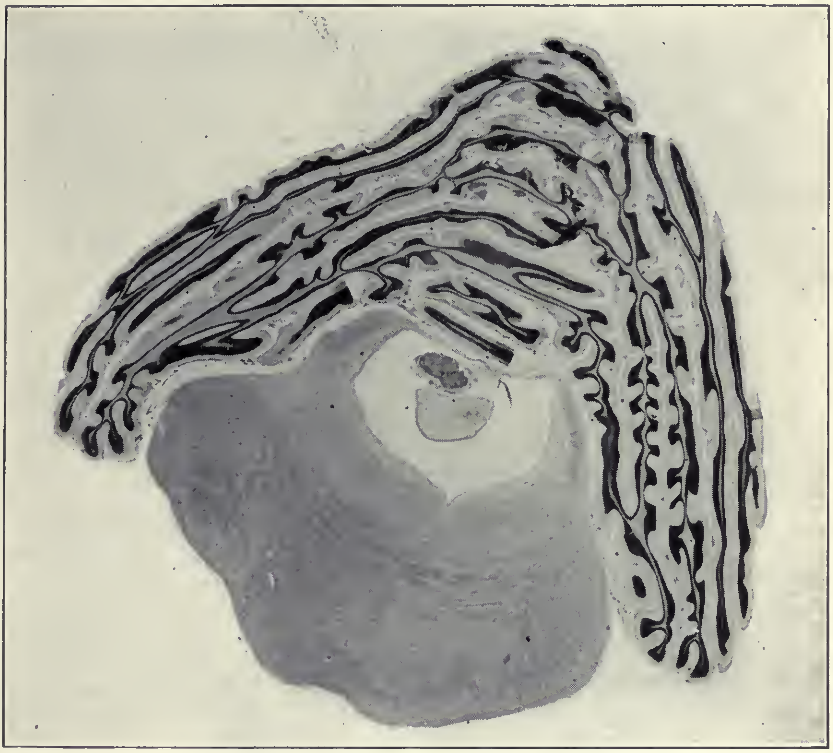


Fig. 3 (Case 5).—Dilated aqueduct of Sylvius showing wall of cyst of the fourth ventricle.

Microscopic Diagnosis: Glioma (astrocytoma) of the cerebellum and the medulla.

Localization of Tumor: Subpial neoplasm of the cerebellum, involving the right cerebellar hemisphere, vermis, medulla and pons; compression of the medulla and the first cervical segment of the spinal cord.

Case 6.—S. K., boy, aged 7 weeks, was admitted to the Babies' Hospital, Jan. 16, 1914, because of a "large head." An increase in size was first noticed at about 2 weeks of age. The child was a full term baby, and the birth was normal. At birth he weighed 6 pounds and 5 ounces. At 2 weeks of age it was noticed that his head was growing too large. At 2½ weeks of age the white of the eye began to show, and at about the same time it was noticed that the veins of the scalp began to be prominent. Vomiting for the first time began at about 5 weeks of age; at times it was forcible.

Physical Examination.—The child gave the remarkable appearance of a small body suspended from a large head (Fig. 4). The head was enormous. It measured 51 cm. (20¼ inches). All the sutures were wide open. The lambdoid measured 30.5 cm. (12 inches), and the sagittal suture, 34 cm. (12½ inches).

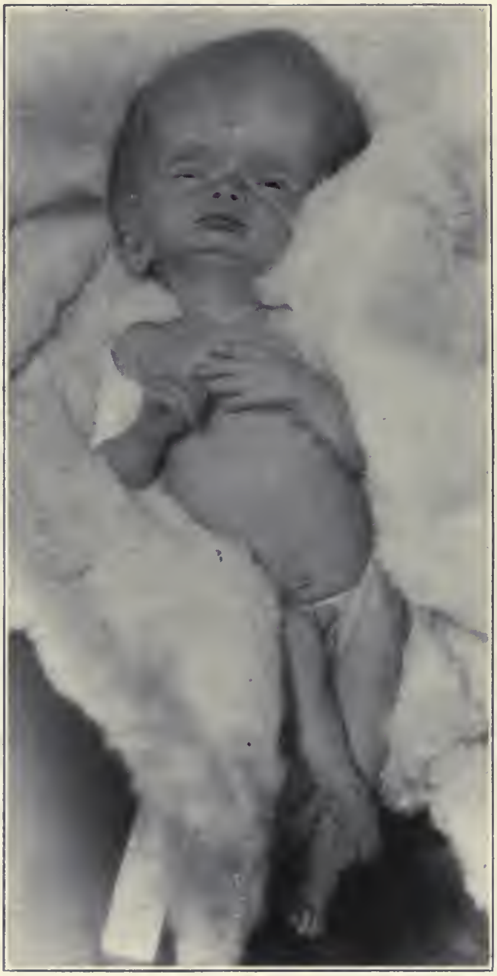


Fig. 4 (Case 6).—Large head and emaciated body of 8 weeks old infant with glioma of the cerebrum.

The scalp was covered by a web of dilated veins (Fig. 5). The palpebral fissure was much widened, exposing the sclera above. Internal strabismus was present. Nystagmus of the rotary type came and went. The liver extended 3 cm. below the costal margin. The knee-jerks were present and active. The head measured 51 cm. (20¼ inches).

Provisional Diagnosis: Internal hydrocephalus.

Course in Hospital.—January 20, the head measured 51.5 cm.

January 23, the head measured 52 cm. The patient was steadily growing weaker. The scalp showed discoloration over the anterior portion, where there was especially pronounced bulging.

January 24, the scalp opened spontaneously in the region of discoloration, and fluid escaped. A hernia cerebri appeared through the rent, which was 9 cm. long.

January 26, the child died.

Necropsy Findings.—Jan. 26, 1914: The body was that of a poorly nourished male child. There were no skin lesions. The head was large and hydrocephalic, measuring 48.5 cm. in circumference. The veins over the scalp were distended. A large hernia cerebri protruded through a tear in the skin of the left frontal region. The prolapsed mass measured 8 cm. by 5 cm. in diameter. Blood-stained cerebrospinal fluid oozed from the protruding mass of cerebral substance. The dura mater showed many punctate hemorrhages, most numerous over the parietal bones.

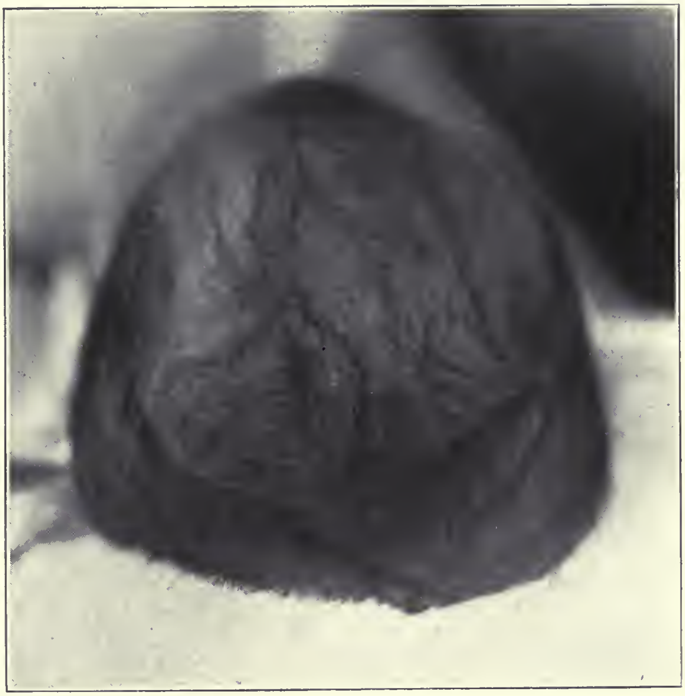


Fig. 5 (Case 6).—Network of dilated veins on the scalp of an infant with glioma of the cerebrum.

The brain was asymmetrical, the left hemisphere being three times as large as the flattened right. The tentorium cerebri was not in the middle line, having been pushed over by the large left hemisphere. The basal fossae were distorted. The left anterior fossa was twice as large as the right, but in the middle and posterior fossae the difference was less pronounced.

The olfactory lobes were thin and flattened, and so was the whole optic commissure. The entire left hemisphere was filled with the new growth, which. on section, showed many recent hemorrhages, softened areas and yellow streaks of old hemorrhages.

A mass weighing 145 gm. broke off from the portion protruding anteriorly. The cortex on the left side covered the neoplasm like a thin shell only 1 cm. in thickness. The right hemisphere showed some flattening of its convolutions and dilation of its lateral ventricles.

The cerebellum was flattened to one-half its normal size. The medulla and pons were also flattened. The fourth ventricle was not dilated.

The left hemisphere measured 19.5 by 14 by 3 cm.; the right 16.5 by 8.5 by 7.5 cm.

Anatomic Diagnosis: Central neoplasm of the cerebrum; hernia cerebri; hydrocephalus; compression of the cerebellum, pons, medulla and optic tract.

Microscopic Examination.—The tumor was composed of round cells with a comparatively small body and a large nucleus, staining deeply. Many mitotic nuclei were present. The cells were very closely arranged, and processes or fibrils were numerous; they could be seen clearly in the edematous parts of the tumor.

There were many blood vessels with very thin walls. The cells were arranged around the vessels, but had no connection with the cells of the vessel walls. In some areas the cells were spindle shaped, but the majority everywhere were round. Areas of necrosis were apparent.

From the number, small size and close packing of the cells, the section gave the appearance of glioma sarcomatoides (Borst) or gliosarcoma. Its origin was probably in the substance of the left hemisphere. Sections through the left lateral ventricle showed a portion of the choroid plexus in the form of cellular villi carrying small blood vessels and covered with epithelial cells.

Sections through the left cerebral cortex showed edema and a diminished number of nerve cells when compared with sections through the same area of the right cortex.

Localization of Tumor: Central neoplasm of the cerebrum; compression of the cerebellum, pons and medulla and optic tract; hydrocephalus; hernia cerebri.

TABLE 8.—Laboratory Findings in Case 6

Spinal Fluid:	January 19—Culture	Negative
	January 21—Color	Yellow
	Pressure	Increased
	Cells	130
	Polymorphonuclears	63 per cent.
	Lymphocytes	37 per cent.
	Fehling's test	+
	Globulin	++
Blood Test:	January 20—Wassermann test	Negative
	January 18—Pirquet test	Negative

Case 7.—R. S., girl, aged 10 months, was admitted to the Babies' Hospital, Sept. 22, 1917, because of vomiting which began about three weeks before admission. The parents were healthy. There was one other child, who was healthy. The birth was normal. She had been breast fed to the present. Whooping cough occurred at 6 months of age. Vomiting began about three weeks previously, following a slight fall on the floor. Irritability began about seven days previously and was noticed when the child was handled. Drowsiness had been noted for four or five days. The eyes had looked "peculiar" for three weeks; no squint and no nystagmus were noticed. Constipation had been present for one week. There were no convulsions, no pain and no retraction of the head.

Physical Examination.—The child was well developed and well nourished but appeared acutely and chronically ill. She was very restless and constantly made purposeless movements of her arms and legs or assumed a cataleptic position. Twitching of the hands and legs was noted at times. There was bulging of the fontanel (3 by 3.5 cm.). There was irregular strabismus, but usually, right external. No nystagmus was noticed. The eyes were fixed and glassy. There was no rigidity of the neck and no retraction. The extremities were rather spastic; there was no paralysis. The knee-jerks were exaggerated; the Babinski and Kernig signs were present.

Provisional Diagnosis: Tuberculous meningitis; brain tumor.

Course in Hospital.—September 26, since admission there had been but little change in the child's condition except that she was growing weaker. The nervous symptoms were the same as on admission. The patient constantly moved her hands and arms or assumed a cataleptic position. There was slight flattening of the left side of face.

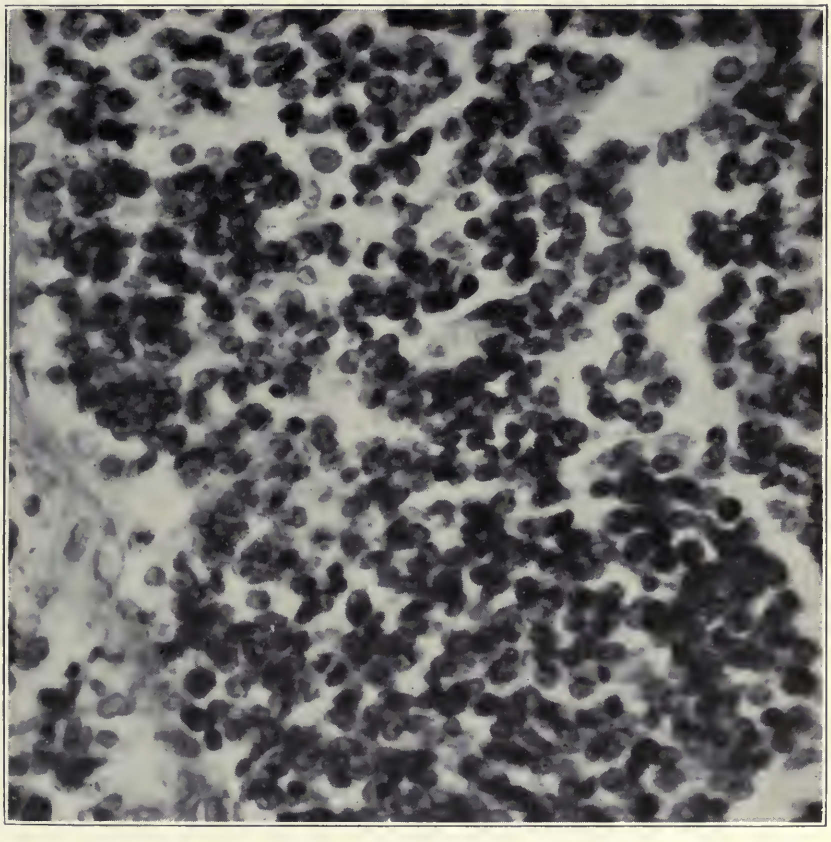


Fig. 6 (Case 6).—Glioma sarcomatoides of cerebrum in infant, 8 weeks old.

September 28, the child died suddenly.

Necropsy Findings.—Sept. 28, 1917: The body was that of a well developed, well nourished white baby girl. The anterior fontanel admitted three fingers. There was moderate craniotabes, but no beading of the ribs and no skin lesions. The dura and the pia-arachnoid presented nothing abnormal. The cerebral hemispheres were normal in appearance, and no lesion was apparent over the brain cortex. At the base there was a neoplasm in the inferior vermiform process of the cerebellum, flattening the medulla and about 1.5 cm. of the cervical cord and pushing the medulla and the pons to the right. The growth measured 4.5 by 3 by 3 cm. It occupied the entire length and breadth of the vermiform process, extended into the middle cerebellar peduncle and into the right cerebellar hemisphere to a distance of about 2 cm. Viewed from above, the tumor was more prominent on the right side of the cerebellum; looked at from below it showed more prominently on the left side, and had displaced the medulla, distorting the fourth ventricle. The growth was rather soft, and on section it was pink, with small hemorrhages and one softened area, 0.5 cm. in diameter. All the ventricles and the aqueduct of Sylvius were dilated moderately. The cerebral cortex was not thinned.

Anatomic Diagnosis: Subpial glioma of the cerebellum, involving the vermis, the right cerebellar hemisphere and the cerebellopontile peduncles; hydrocephalus; compression of medulla and upper segment of the cervical cord.

Microscopic Examination.—The tumor is a glioma (astrocytoma) with comparatively large blood vessels.

TABLE 9.—Laboratory Findings in Case 7

Spinal Fluid:	Sept. 23, 1917	Sept. 26, 1917
Amount	—	20 c.c.
Color	Clear	Clear
Pressure	Increased	—
Cells	24 (lymphocytes, 100%)	90 (polymorphonuclears, 9%; lymphocytes, 91%)
Globulin	0	0
Sugar	0	+
Blood Test:		
Wassermann test	Negative	
Pirquet test	Negative	
Blood Examination:		
Leukocytes	13,000	
Polymorphonuclears	33 per cent.	
Lymphocytes	67 per cent.	
Eye Grounds:		
Blurring of mesial side of both disks, more marked on right side		

Localization of Tumor: Subpial glioma of the cerebellum, involving the vermis, the right cerebellar hemisphere and the cerebellopontile peduncles; hydrocephalus; compression of the medulla and upper segment of the cervical cord.

SUMMARY

1. In seven cases of tumor of the brain in children between the ages of 2 weeks and 3 years, the average age was 15 months.
2. All the tumors were gliomatous in type.
3. Two were supratentorial and five were infratentorial.
4. Of the supratentorial tumors, one occupied the left cerebral hemisphere and was congenital in origin. The other occupied the basal ganglions.
5. In the five infratentorial tumors the vermis of the cerebellum was involved. The growth involved the right cerebellar hemisphere in four and the left hemisphere in only one instance. The medulla and the pons were infiltrated in two cases, and the right cerebellopontile peduncle was involved in two instances. The upper cervical cord was compressed in three of the cases.

6. Hydrocephalus was present in each of the seven cases.

7. The most striking feature of the symptomatology is the variability in physical signs.

8. Convulsions were absent in all cases except one in which a convulsion occurred just before death.

9. Vomiting did not appear as a significant symptom in any of the cases.

10. The spinal fluids showed nothing that is distinctive. Xanthocromia was present in only one case in which there was a cerebral hernia.

THE CHARACTERISTICS OF THE CEREBROSPINAL FLUID IN POSTDIPHTHERIC PARALYSIS

JOSEPH C. REGAN, M.D., CATHERINE REGAN, M.D.
AND
BRICKHOUSE WILSON, M.D.
BROOKLYN

The characteristics of the spinal fluid in postdiphtheric paralysis has received scant attention in our own literature. There were no observations published in this country, as far as we could ascertain, until the report made previously by one of us (J. C. R.). Foreign workers, especially French clinicians, have published their investigations in a small number of cases. There has not been accumulated as yet, however, a sufficient amount of information on the subject to establish conclusively the cytologic and chemical alteration, if any, which may be encountered.

An exact knowledge of the condition of the spinal fluid in postdiphtheric paralysis is of some importance for two reasons: first, to determine the presence or absence of a reaction on the part of the meninges to the toxins of the diphtheria bacillus, and second, to assist in the differential diagnosis of this condition from certain other diseases which may be accompanied or followed by paralytic symptoms.

The disease clinically which is probably most likely to be mistaken for postdiphtheric paralysis is acute poliomyelitis. The difficulties of differentiating the two may be so great, under certain conditions, as when the history of initial angina is lacking or overlooked, that a positive diagnosis may only be assured by the course of the paralytic symptoms, and in fatal cases, in exceptional instances, by the examination of microscopic sections of the central and peripheral nervous system at necropsy. Yet an examination of the spinal fluids shows different characteristics in the two maladies.

There are other conditions with which diphtheric multiple neuritis is at times confused clinically. Briefly, these are capillary bronchitis, lobar pneumonia, laryngeal diphtheria, tabes dorsalis, epidemic encephalitis and the multiple neuritis following other infectious diseases, such as scarlet fever and measles. The details of the differential diagnosis of the disease will not be spoken of in this publication, as we are concerned primarily with the spinal fluid findings.

---

* Received for publication, Feb. 2, 1923.

* From the Kingston Avenue Hospital, Bureau of Hospitals, Department of Health, New York, Dr. R. J. Wilson, Director, and Dr. W. T. Cannon, Physician in Charge.

Certain previous reports have been made on this subject. De Massary,[1] Marfan,[2] Dufour,[1] Comby [1] and Netter [3] have failed in their cases to find any evidence of a meningeal reaction, as shown by an increased albumin content or lymphocytosis of the spinal fluid. On the other hand certain investigators have published cases in which they found a distinct lymphocytosis, with usually also an associated augmentation of albumin. Single cases in which such changes were observed are reported by Rohmfeld,[3] Chauffard and Le Conte,[3] Ravaut and Krolinetsky,[4] and Hallez and Lortat-Jacob.[5] De Lavergne [6] and others have noted instances in which there was a dissociation between the albumin which was augmented and the cells which were normal. The series of six cases with ten specimens of spinal fluid previously reported [7] by one of us (J. C. R.) showed alteration in only one instance by a 3 + albumin and a 2 + globulin reduction.

The present series comprised a total of sixteen patients and twenty-eight specimens of spinal fluid which were examined at intervals after the onset of the angina, varying from the sixteenth day to the thirteenth week and from the second day after paralysis had supervened to the eleventh week thereafter. Divided into groups according to the week of the paralysis on which the puncture was performed, these specimens of spinal fluid may be classified thus: first week, eight; second week, five; third week, five; fourth week, four; fifth week, two; sixth week, one; seventh week, one; eighth week, one; eleventh week, one.

The initial angina had been, in most instances, a moderately or very severe type with membrane involving the tonsils, uvula, pillars of the fauces, often also the soft palate, nasopharynx, nose and larynx. The diphtheria bacillus was usually associated with other microorganisms representing thus the polymicrobian, septic or mixed infectious form of the disease, with its characteristic heavy, thick, dark-

---

[1] Discussion in Bull. et mém. Soc. méd. d. hôp. de Paris **45**:1097 (July 15) 1921, on Merklen, P., Weiss, M., and de Gennes, L.: Ibid. **45**:990 (July 1) 1921.

[2] Marfan, A. B.: Leçons cliniques sur la diphthérie et quelques maladies des premières voies, Paris, 1905, p. 216.

[3] Discussion on Chauffard and Le Conte; Paralysies nucléaires multiples d'origine diphtérique avec réaction meningés, Bull. et mém. Soc. méd. d. hôp. de Paris **39**:997 (Nov. 12) 1915.

[4] Ravaut, P., and Krolinetsky, G.: Paralysie diphtérique généralisée avec réaction méningée Bull. et mém. Soc. méd. d. hôp. de Paris **40**:913 (June 9) 1916.

[5] Hallez, G. L., and Lortat-Jacob: Le liquide céphalorachidien dans les paralysies diphtériques, Bull. et mém Soc. méd. d. hôp. de Paris **41**:1259 (July 6) 1917.

[6] De Lavergne, M.: De l'altération du liquide céphalorachidien dans les paralysies diphtériques du voile du palais et à type de polyneurite, Bull. et mém. Soc. méd. d. hôp. de Paris **44**:1246 (Oct. 22) 1920.

[7] Regan, J. C.: Postdiphtheritic Paralysis and the Spinal Fluid Findings, Arch. Pediat. **35**:641 (Nov.) 1918.

SUMMARY OF CASES WITH SPINAL FLUID FINDINGS

Age; Case No.; Date of Admission	Type of Diphtheria	Day of Disease Antitoxin Was First Given	Amount of Antitoxin		Day of Disease Paralysis Supervened	Distribution of Completely Developed Paralysis	Day of Disease Puncture Performed	Colloidal Gold Reaction	Cell Count per C. Mm.	Globulin	Fehling's Reaction	Other Complications	Outcome
			Before Admission in 1,000 Units	After Admission in 1,000 Units									
3 yrs. 814 3/15/22	Pharyngeal, nasal and sepsis	14th	..	40	19th 27th	Early: palate, larynx, cardiac arrhythmia. Later weakness lower extremities and back	29th	1 2 2 2 2 0 0 000	7	—	3+	Myocarditis nephritis, heart block	Died 4/10
3½ yrs. 1970 9/26/20	Pharyngeal, nasal	3d	..	30	16th 35th	Early: palate, cardiac arrhythmia. Later: upper and lower extremities, pharynx, strabismus	44th	1 1 2 2 3 3 3 200	3	1+	3+	Nephritis	Recovered
4 yrs. 584 2/25/22	Pharyngeal, nasal and sepsis	4th	10	35	14th 37th	Early: palate. Later: upper and lower extremities, back, neck, pharynx, diaphragm (weak)	16th 22d 37th	1 1 1 1½ 1½ 1½ 0 000 1 1 1 1 0 0 0 000 1 1 2 2 2 1 0 000	5 2 0	— — —	3+ 3+ 3+	....	Died 4/1/22
1½ yrs. 697 3/6/22	Not observed; ill 5 weeks on admission	..	..	..	Approx. 3d week	Palate, pharynx, partial upper and lower extremities, strabismus, left facial, diaphragm (partial), atelectasis lower lobe both lungs	4th wk. 6th wk. 8th wk. 9th wk. 11th wk.	1 1 1½ 2 2 0 0 000 1 1 1½ 2 2 1 0 000 2 2 2 3 3 2 0 000 1½ 2 1 1 1½ 0 0 000 0 0 0 0 0 0 0 000	2 10 7 2 0	2+ 1+ — — —	3+ 3+ 3+ 3+ 3+	Myocarditis	Recovered
5 yrs. 183 2/25/22	Pharyngeal, nasal and sepsis	4th	10	25	12th 16th 27th	Early: cardiac arrhythmia, palate and left lower extremity. Later: pharynx, larynx, back, neck, bulbar	20th 28th 35th	1 1 1 1½ 1½ 1½ 0 000 1 1 2 2 2 1 0 000	2 2 5	— 1+ —	3+ 3+ 3+	Myocarditis, nephritis	Recovered
5 yrs. 1811 9 16 '21	Not observed; ill 5 weeks on admission	1st wk.	unknown	..	2d wk. 4th wk.	Early: palate. Later, lower extremities, larynx, weakness neck and back	5th wk. 8th wk. 13th wk.	0 ½ 0 ½ 1 2½ 2½ 2 0 ½ 000 5 0 0 0 1½ 1 0 000 0 0 0 0 0 0 0 000	6 7 2	1+ 1+ —	3+ 3+ 3+	....	Recovered

4 yrs. 823 3/16/22	Pharyngeal, laryngeal	3d	..	30	17th	Cardiac arrhythmia, slight pharyngeal	26th	0 0 0 0 0 0 0 000	5	—	3+	Intubation, myocarditis	Recovered
4 yrs. 1851 9/28/22	Pharyngeal, nasal and sepsis	2d	15	20	9th	Early: palate. Later: pharynx, strabismus, lower extremities, back, cardiac arrhythmia	35th 50th	1 1 1 1 1½0 0 000 1 1 1 1 1 0 0 000	10 5	± ±	3+ 3+	....	Recovered
4 yrs. 861 3/20/22	Pharyngeal, nasal and laryngeal	3d	20	20	27th 32d	Early: palate, cardiac arrhythmia. Later: pharynx, larynx, bilateral strabismus, right ptosis, back and lower extremities	33d	2 2 2 3 3 2 2 11	2	—	3+	Myocarditis, intubation	Recovered
4 yrs. 860 3/20/22	Pharyngeal, laryngeal and sepsis	3d	15	30	13th 24th	Early: pharynx, palate, cardiac arrhythmia. Later: larynx, diaphragm, abdomen, strabismus	34th	1½2 3 3 2 ½0 000	2	±	3+	Myocarditis	Recovered
7 mos. 1657 6/7/22	Not observed	14th	10	..	11th 21st	Early: palate. Later: strabismus (right), pharynx, larynx	22d	2 2 2 1 1 0 0 000	7	—	3+	Broncho-pneumonia, intubation	Died 6/10
3 yrs. 1289 5/23/22	Pharyngeal ?, ill 3 weeks on admission	..	..	..	7th	Early: palate. Later: neck, back, bilateral strabismus, diaphragm	22d 25th	1 1 2 2 1 0 0 000 1 2 2½2 1½0 0 000	2 0	— —	3+ 3+	Broncho-pneumonia, myocarditis	Died 5/25
3 yrs. 823 3/6/22	Pharyngeal, laryngeal	6th	15	30	12th	Early: palate and pharynx	12th	2 2 3 ½ ½0 0 000	5	—	3+	Br.pneu., myocarditis, aph. stom., intubation	Recovered
7 yrs. 2253 12/21/22	Pharyngeal, nasal and sepsis	5th	..	40	26th	Early: palate. Later: left facial, cardiac arrhythmia	29th	1 1 1 1 0 0 0 000	5	—	3+	Myocarditis	Recovered
4½ yrs. 856 3/19/22	Pharyngeal, nasal and sepsis	2d	10	20	17th	Early: cardiac arrhythmia. Later: double internal strabismus	22d	1 1½2 1 0 0 0 000	0	—	3+	Myocarditis	Recovered
4 yrs. 1479 5/17/22	Nasal (child ill 1 month with slight aphonia, previous to which for an indefinite period there was a nasal discharge	..	..	..	unknown	Early: larynx. Later: right facial, palate, pharynx, weakness upper extremities, left intercostals and diaphragm	5/20 5/26	2 2 2 1 0 0 0 000 2 1 1 1 0 0 0 000	2 2	— —	3+ 3+	Otitis media, measles, pneumonia	Recovered

colored membrane, serous nasal discharge, cervical adenitis and periadenitis. One of the patients had a pure nasal diphtheria of indefinite duration which had never been recognized until the development of paralytic symptoms.

The paralysis was generalized in ten patients, was limited to an involvement of the pharynx in one, to the palate and pharynx in one, to the palate and left side of the face in one, to the palate, pharynx, larynx, extrinsic muscles of the eyes, diaphragm and abdominal wall in one, to the extrinsic muscles of the eyes, pharynx, larynx and palate in one, and to the extrinsic muscles of the eyes only in one. A cardiac arrhythmia was noted in a number of cases.

The punctures were performed with the aseptic technic of a major operation. The fluid was removed slowly with the child always in the prone position, and usually only from 5 to 10 c.c. was withdrawn.

The fluid was clear in all instances, of normal limpid watery transparency, and under normal or slight hypertension. A Bordet-Wassermann reaction was performed at least once on the spinal fluid of each patient, and the results were uniformly negative. The cell count was in every instance within normal limits, as will be seen in the accompanying table. The Fehling's reaction was normal in each fluid, namely a 3 + reduction, indicated by an immediate and heavy precipitate. In only two ways did the rachidian liquids show any abnormality. One was in the almost constant presence of a positive colloidal gold reaction in the syphilitic zone, and the other was in the occurrence in nine fluids from six patients of globulin varying in amount from a ± to a 2 + reaction.

No clear relationship could be shown between the type of the disease or its outcome and the presence of globulin in the spinal fluid. As shown by the table the globulin reaction was usually only mildly positive (1 +) and occurred in only about one third of the patients. The globulin seemed to diminish as convalescence was established and the paralysis disappeared.

The colloidal gold reduction was commonly confined to the first five or six dilutions (1 : 10 to 1 : 320) ; but in two instances it reached well into the meningitic zone (Cases 1970 and 861). In one instance (Case 823) there was no reaction, this patient having only a localized mild paralysis.

As the patients improved clinically the reaction seemed gradually to subside, and in two patients (Cases 697 and 1811), followed to the eleventh and thirteenth weeks of the disease, respectively, the curve had reached the normal level. This is the first report, we believe, of the results obtained by the employment of the colloidal gold reaction in postdiphtheric paralysis.

SUMMARY

To determine whether a meningeal reaction occurs in the spinal fluid in postdiphtheric paralysis, and to assist in establishing the cytologic and chemical formula in that disease, which is of importance at times in differential diagnosis, a study of the rachidian liquid was carried out. A series of twenty-eight specimens of spinal fluid from sixteen patients were examined at various intervals, from the second day to the eleventh week of the paralysis, twenty-two being in the first four weeks. Nearly two thirds of the patients had extensive generalized paralysis, and in five death supervened. These paralyses followed usually a moderately or very severe initial angina commonly of a polymicrobian or septic form, with extensive membrane formation and frequently accompanied by myocarditis.

CONCLUSIONS

From the results of the examination of the spinal fluid in a previous series and in the present one, we feel that the following tentative conclusions may be drawn:

1. The cerebrospinal fluid in postdiphtheric paralysis is a clear limpid liquid, flowing usually under normal or slight hypertension.
2. The Bordet-Wassermann reaction of the spinal fluid was uniformly negative in each case.
3. The cell count was always within normal limits, less than 10 cells per c.mm., and the cells found were small lymphocytes.
4. The globulin was increased in a minor proportion of the patients, less than one third. The increase was slight, occasionally moderate, never marked.
5. There existed, therefore, in certain cases (less than one third) a dissociation between the cytologic and chemical findings.
6. The colloidal gold reaction was the most constantly positive pathologic reaction encountered in the fluid of this disease. The reduction usually occurred in the syphilitic zone, occasionally extending into the higher dilutions. The reaction seemed gradually to subside, reaching normal as convalescence was established and paralysis disappeared.

TRANSFUSION THROUGH THE UMBILICAL VEIN IN HEMORRHAGE OF THE NEW-BORN

REPORT OF A CASE

J. BUREN SIDBURY, A.M., M.D.
Attending Pediatrician, James Walker Hospital; Consulting Pediatrician,
Community Hospital (Colored); Attending Pediatrician,
Babies' Hospital, Wrightsville, N. C.
WILMINGTON, N. C.

The use of human blood as a therapeutic agent in melena or hemorrhagic disease of the new-born has been one of the gratifying advances in medicine during the last decade. Human blood has acted as a specific in this condition.

HISTORY

The first transfusion of blood for hemorrhagic disease of the new-born was performed in New York City by Dr. Alexis Carrel in 1908.[1] The method was direct transfusion from the left radial artery to the right popliteal vein. The baby recovered. In 1909 Dr. Crile introduced the cuff and cannula method. In 1910 the Elsberg cannula was introduced, and, during the same year, Vincent of Boston introduced the method employing the paraffin coated glass tubes.

In 1913 Lindemann aroused considerable interest in transfusion by introducing the syringe method, which simplified the procedure and, at the same time, gave a method by means of which the quantity given could be accurately measured.

In 1915 Lewisohn [2] reported two cases in which transfusion was performed by the citrate method. Since then many modifications of these methods have been reported with good results in all. For the sake of brevity, they can be divided into two general groups, namely, direct and indirect. In one treated blood is used and in the other untreated blood.

In 1908 the first case of hemorrhagic disease of the new-born was treated by subcutaneous injection of whole blood by Schloss. Between 1908 and 1911, seven such cases were treated by him with one death.[3] In 1910 Welch [4] reported twelve cases treated by transfusion. Since then a large number have been so treated with good results.

ROUTES

In infants the routes that have been used are the superficial veins of the arm, of the neck, of the scalp and the popliteal or femoral vein.

---

* Received for publication, Feb. 5, 1923.

[1] Lambert: Med. Rec. **73**:883 (May) 1908.

[2] Lewisohn, R.: Surg., Gynec. & Obst. **21**:37 (July) 1915.

[3] Schloss, O. M., and Commiskey, L. J. J.: Spontaneous Hemorrhage in the New-Born, Am. J. Dis. Child. **1**:276 (April) 1911.

[4] Welch: Am. J. M. Sc. **139**:800, 1910.

In September, 1915, Helmholz[5] was the first to bring to our attention the employment of the superior longitudinal sinus as a route for the aspiration of blood as well as for injections. In the same year, Howard[5] used the superior longitudinal sinus, injecting citrated blood. Since then this route has been used frequently on account of its accessibility in very young infants. In 1919 I used the umbilical vein in an infant 4 days old, giving 100 c.c. of whole blood by the syringe method, with satisfactory results.

ETIOLOGY

The etiology of this condition is not known. The following factors are thought to have some bearing:

1. Hypoplasia of the coagulating elements of the blood may be a factor. According to Schloss and Commiskey,[6] "the cause for persistent bleeding in these cases must be due to some defect in the normal mechanism of the blood clotting time." They report ten cases which showed a coagulation time varying from normal to indefinite times, showing that the bleeding is not always dependent upon hemorrhagic diathesis. Another interesting point here is that the injection of blood cures these patients immediately and they have no return of symptoms. Transfusions do not cure patients with hemophilia.

2. From 2 to 6 per cent. of these cases are syphilitic, according to Holt.

3. Infection seems to act as a predisposing factor.

4. From observation, we note that babies that have been more or less asphyxiated have a tendency to bleed.

5. Trauma, such as is frequently suffered in difficult deliveries, and the common methods of resuscitation may well be exciting causes.

Rodda[7] has called our attention to the fact that as many as 50 per cent. of the necropsies in cases of stillbirth or on infants that die a few days after birth reveal hemorrhages in different parts of the body, many of which were not recognized before death.

According to Brown and Swift,[8] these cases may be divided into three clinical types, namely: the umbilical, the seromucous, and the purpuric, with a mortality of 60, 50 and 22 per cent., respectively. This was before the use of serum and blood transfusion.

---

[5] Helmholz, H. F.: The Longitudinal Sinus as the Place of Preference in Infancy for Intravenous Aspirations and Injections, Including Transfusion, Am. J. Dis. Child. **10**:194 (Sept.) 1915. Howard, W. S.: A Simple Method of Transfusion in Hemorrhage of the New-Born, J. A. M. A. **65**:1365 (Oct. 16) 1915.

[6] Schloss, O. M., and Commiskey, L. J.: The Etiology and Treatment of the So-Called Hemorrhagic Disease of the New-Born, Am. J. Dis. Child. **3**:216 (April) 1912.

[7] Rodda, F. C.: Coagulation Time of Blood in the New-Born, J. A. M. A. **75**:452 (Aug. 14) 1920.

[8] Brown and Swift, cited by Lespinasse, V. D.: The Treatment of Hemorrhagic Disease of the New-Born by Direct Transfusion of Blood, J. A. M. A. **62**:1866 (June 13) 1914.

Rodda[7] has shown that these babies have a prolonged bleeding time as well as a delayed coagulation time. This may be increased up to fifteen or twenty minutes, and, in some cases, even longer.

OCCURRENCE

At the Boston Lying-In Hospital, Townsend[9] reported that bleeding in the new-born occurred in thirty-two infants in 5,000 births. Ritter found 190 cases among 13,000 births at the lying-in hospital at Prague. Epstein found that it occurred in 8 per cent. of the cases at the New York Foundling Hospital. From Rodda's recent article, we must conclude that these figures are based mainly on clinical diagnoses, and that the occurrence is a great deal more frequent than their figures would indicate. Rodda[7] states that "statistics from the New-Born Clinic, University of Minnesota, show that postmortem examinations reveal cerebral hemorrhage in more than 50 per cent. of all infants that die inter partum or during the first few days of life. These findings often were made following noninstrumental, or even easy, deliveries." It was also noted that these hemorrhages occurred in other organs than the brain.

Here I want to emphasize one very important point. If these babies bleed they bleed early. The vast majority of them bleed within the first forty-eight or seventy-two hours, and practically all of them bleed within the first week of life. Lespinasse[10] reported fifteen cases treated with transfusion, and all but two patients were less than 4 days old. The umbilical vein is patent and accessible up to 4 days of life, as demonstrated by my case.

MORTALITY

Before the use of human blood, the mortality in this condition was from 35 to 87 per cent.[3] Up to 1914, thirty-seven cases had been reported treated with human blood, either by injection under the skin, or by transfusion, or by both, with three deaths, or a mortality rate of 8 per cent. We now believe that all of them should recover if properly treated.

TREATMENT

Lucas and Dearing[11] by the vital dye method demonstrated that the blood volume in infants was about one tenth of the body weight. If we use this as a basis, an infant has 1 ounce of blood to each pint in the adult. If we bear this relationship in mind, we may better appreciate what the loss of a few ounces of blood means to an infant. Any bleeding in the new-born baby should put us on our guard to the extent of securing a donor in case an immediate transfusion becomes necessary. In any event it is advisable to give a subcutaneous injection of from 15 to 20 c.c. of whole blood and repeat this in six or eight hours. If there is any further evidence of bleeding, transfusion should be repeated. In the intestinal case, the external manifestation is no index of the amount of blood lost. The baby may become exsanguinated by bleeding into the intestinal tract, and only a small dark stool may be seen or even no stool at all. In these cases, immediate transfusion is the only hope.

---

[9] Townsend, cited by Cherry, T. H., and Langrock, E. G.: The Relation of Hemolysis in the Transfusion of Babies with the Mothers as Donors, J. A. M. A. **66**:626 (Feb. 26) 1916.

[10] Lespinasse, V. D. (Footnote 8).

[11] Lucas, W. P., and Dearing, B. F.: Blood Volume in Infants Estimated by the Vital Dye Method, Am. J. Dis. Child. **21**:96 (Jan.) 1921.

It was once thought that the blood of the mother and of the infant were always compatible. Cherry and Langrock[12] tested thirty-four new-born babies against their mothers' blood. There was no agglutination nor any hemolysis in any of these tests. They started out to make 100 consecutive tests on as many babies born in the hospital, but they stopped when thirty-four gave no agglutination and no hemolysis.

According to the more recent work of Jones[13] on 197 specimens of blood from young infants, 78.8 per cent. could be placed in one of four groups in accordance with the classification of Moss. He showed that the different groups occurred with approximately the same frequency in the new-born infant as they do in the adult. Iso-agglutinins have been demonstrated in the blood of a 7 months' fetus.

In 1920 Minot and Weld[14] examined 160 specimens of umbilical cord blood and found that 70 per cent. could be definitely grouped.

Happ[15] established the group by both serum and cell reaction in 22.7 per cent. of infants between 1 and 3 months of age, in 31.8 per cent. of infants from 4 to 6 months, and in 69.7 per cent. of infants from 6 months to 1 year. He states that after one year the group could be established in practically every case.

Unless time will not permit, every patient should be tested against the donor for agglutination and hemolysis before the transfusion is performed. Of course, the Wassermann reaction of the donor's blood should be known.

The injection and transfusion of whole blood will accomplish these results: (1) stop the hemorrhage; (2) replace lost blood, and, (3) overcome infection by giving new antibodies and new complement.

---

[12] Cherry, T. H., and Langrock, E. G. (Footnote 9).

[13] Jones, B. B.: Iso-Agglutinins in the Blood of the New-Born, Am. J. Dis. Child. **22**:586 (Dec.) 1921.

[14] Minot, G. R., and Weld, M., cited by Jones, B. B. (Footnote 13).

[15] Happ, W. M.: J. Exper. Med. **31**:313 (March) 1920.

REPORT OF CASE

A boy, well nourished and well developed, was born, March 5, 1919, at 3 p. m., after normal labor, at the end of the fourth pregnancy. The baby weighed 9 pounds. There was no cyanosis, no jaundice and no history of any hemorrhagic tendency in the family. Three other children were living and well.

Very soon after the delivery, a dorsal slit was made on the penis, and the attending physician went to town, 12 miles away. Four hours later, the nurse telephoned the physician that there was bleeding from the incision in the penis. The incision was sutured tight, and a number of local applications to stop bleeding were applied during the next thirty-six hours, but to no avail. The baby was brought to the hospital the second day in very poor condition. Bleeding from the dorsal slit incision continued; the baby was pale and looked as if he had lost considerable blood. He noticed very little that went on around him. He was given 15 c.c. of whole blood from the father. This injection was repeated in eight hours. At the time of the second injection, the bleeding had practically ceased. Twelve hours later the blood injection was repeated, though there had been no bleeding since the second injection. At this time the baby's blood showed hemoglobin, 25 per cent.; erythrocytes, 2,000,000; coagulation time, fifteen minutes. We were unable to determine the bleeding time. The baby had taken very little food and took water only by means of a medicine dropper. A transfusion of blood was decided to be advisable. The mother was brought to the hospital, and the baby was given 100 c.c. of whole blood by way of the umbilical vein. The cord was kept wet with a saturated boric acid solution for eight hours before the transfusion, or during the time required to bring the mother to the hospital and to perform the transfusion.

COMMENT

Obtaining blood from one of the superficial veins of the new-born infant is often a difficult task and at times even impossible in the hands of an expert. The easiest route is by way of the superior longitudinal sinus; but this route should be employed only by one experienced in its use, and even the experienced worker may fail to enter the sinus because of its abnormal position, due to distortion from molding of the head. This is especially true during the first few days of life. We must admit also that the cranial cavity cannot be punctured with impunity: calamity will sooner or latter ensue.

The psychic effect on the mother was one of the reasons for selecting another route than that by way of the superior longitudinal sinus in this case. I dare say that no mother could look on with impunity and see a needle thrust into her baby's head. To avoid this psychic effect on the mother, I chose this new and different route.

So far as I know this method has never been used before; but it appealed to me as a rational method for the baby had been receiving blood and nourishment through the umbilical vein exclusively until three days previously. I gave him 100 c.c. of blood through this channel. At the time I thought of the possibility of a clot in the umbilical vein; but I felt that its occurrence was unlikely in this type of case for we know that the blood from these patients remains in a fluid state for a long time when withdrawn from the body and kept in contact with foreign substances. Since then I have performed necropsies in two cases of hemorrhagic disease of the new-born and dissected out the umbilical vein to its entrance into the liver. It was perfectly smooth and clean throughout; no blood was present.

METHOD OF TRANSFUSION

The umbilical cord stump, which was of the usual length, about 2 inches, was surrounded by a gauze dressing which was kept wet with sterile saturated boric acid solution. This was continued for eight or ten hours until the mother could be brought to the hospital. This kept the cord from becoming too dry.

The baby was placed on the operating table, and the umbilical cord was exposed. The cut end of the cord presented the two patent lumens of the umbilical arteries and the collapsed umbilical vein, the latter, the largest of the three openings. The cord was then cut just proximal to where it had previously been tied off. This gave a fresh cross-section of these three blood vessels. The regular "record" transfusion needle was inserted into the largest of these three vessels, the umbilical vein, and a ligature was tied over the cord to the needle to hold the needle in place. At this point a 20 c.c. record syringe was filled with physiologic sodium chlorid solution, and this was slowly injected into the umbilical vein. No resistance occurred and no obstruction was noted. An effort was made to withdraw the saline in order to see whether any sudden stoppage of the needle would occur, as the withdrawing of a clot into the needle. That was not noted. After this was done, it was felt that the vein was patent and that it was safe to proceed with the transfusion as planned. At this juncture the mother's arm was prepared as usual, and the median basilic vein was entered with a needle similar to the one used in the baby's vein. With the aid of an assistant who filled the 20 c.c. record syringes with blood from the mother's vein, I gave five 20 c.c. syringefuls of whole untreated blood direct from the mother's veins. After the fifth syringe was emptied in the umbilical vein, I injected 10 c.c. of physiologic sodium chlorid solution to rinse out the needle and the vein. The needle was then withdrawn from the umbilical vein, and the cord was again tied off as before.

If given earlier, this transfusion would have stopped the bleeding; but it was given primarily to replace the blood lost. It was believed that the baby had lost at least 4 or 5 ounces of blood and probably more. It was also believed that the baby was beginning his life with a considerable handicap, having lost probably a third or a fourth of his blood. To replace this lost blood would very probably make his first year uneventful. Following the transfusion, the hemoglobin increased to 80 per cent. and the erythrocytes to 4,500,000. He had a slight chill and a rise of temperature to 103, two hours after the transfusion. The temperature fell immediately, and the baby made an uneventful recovery. He weighed 25 pounds at 12 months, 30 pounds at 2 years, and 38 pounds at 3½ years. He is normal in every way.

SUMMARY

This baby was transfused through the umbilical vein on the fourth day of life with the greatest ease. The fact that the great majority of cases of hemorrhagic disease of the new-born occur during the first three days of life should impress upon our minds the fact that if transfusion is necessary in these infants it may be performed through the umbilical vein with greater ease than by any other route. It is a common observation of Rodda,[16] Warwick[17] and others who have performed necropsies on the new-born that the blood remains fluid hours after death in most of these cases.

Lucas[18] showed that there is a definite prolongation of coagulation time in the first few days. He says, "There is a definite and fairly constant condition in the blood of the new-born which favors the so-called hemorrhagic condition of the new-born." He found the coagulation time prolonged as much as forty minutes. He believes that the new-born infant normally has a prolonged coagulation time, whether hemorrhage appears or not.

CONCLUSIONS

1. The umbilical vein may be patent and accessible for transfusion up to, and including, the fourth day of life.
2. The umbilical vein up to the fourth day is the most accessible vein in a new-born baby, if patent.
3. The probability of a clot in the umbilical vein is very unlikely because the blood is fluid many hours after death in these cases.
4. Transfusion through the sinus in cases of intracranial hemorrhage may increase intracranial pressure, which is not desirable.
5. Transfusion through the superior longitudinal sinus is comparatively simple for one experienced, while the umbilical route is simple for those inexperienced in the sinus route.
6. In my experience, the median basilic vein is always large enough to admit an 18 gage needle in infants as young as 2 or 3 weeks, and is preferable to the superior longitudinal sinus usually; but it is necessary to dissect it out.

---

[16] Rodda, F. C.: Determining Coagulation Time of the Blood in the New-Born, Am. J. Dis. Child. **19**:268 (April) 1920.

[17] Warwick, M.: Necropsy Findings in New-Born Infants, Am. J. Dis. Child. **21**:488 (May) 1921.

[18] Lucas, W. P., et al.: Blood Studies in the New-Born, Am. J. Dis. Child. **22**:525 (Dec.) 1921.

THE CAUSES OF ABSENCE IN A BOYS' SCHOOL *

C. H. SANFORD, M.D.
CONCORD, N. H.

The study here reported was made at St. Paul's School,[1] and is recorded because data concerning the health of schoolchildren are always helpful. In Table 1 are summarized the diagnoses in the various cases, as given in the infirmary records, and the total number of days spent in the infirmary for three consecutive years.

There are several interesting points in this table that should be noted. In the first place it is quite evident that some of the conditions listed are closely related, and a sharp differential diagnosis is often impossible. This is particularly true of the first nine conditions, the respiratory tract infections. The diagnosis was made either from the outstanding condition on admission, or from the development of the disease during the illness. That is to say, if a boy came to the infirmary with coryza, but later developed bronchitis, the diagnosis was given as bronchitis; or if a boy complained of sore throat and later developed an infection of the middle ear, which overshadowed the primary condition, the diagnosis was given as otitis media. If, on the other hand, the chief complaint was coryza, and nothing further developed, the diagnosis remained coryza.

It is quite possible, also, that some of the cases listed under headache should be listed under some other heading, as constipation, sinusitis or fatigue. But in these cases no such causative condition could be found, and they had, therefore, to be classed according to the chief complaint on admission.

It is interesting to note that in many of the cases of indigestion there was a definite history of overeating, showing that this youthful indiscretion is an occasional cause of sickness. In the school year of 1919-1920, there were only two patients that gave such a history; but in 1920-1921 there were nineteen patients, or one third of the total number, causing a loss of fifty-six days. In the following year, there was exactly the same number of cases, with the same number of days lost as in 1920-1921. It is, no doubt, true that some of the other cases were due to the same cause, although no such history could be obtained.

The contagious diseases reveal several interesting points. The usual history of an epidemic of any of the contagious diseases is that it began

---

* Received for publication, Feb. 5, 1923.

[1] A boarding school at Concord, N. H., for boys ranging in age from 11 to 18 years.

in a patient who had returned from a vacation. Occasionally, however, a case arises in the middle of a term, long after the incubation period has passed, and in which no source of contagion can be found. Except for an occasional visit to Concord (2 miles from the school) and an occasional visitor, the school is fairly well isolated, and the points of contact are reduced to the minimum. Within the school, however, the points of contact between boys are numerous, and whenever a case of a contagious disease occurs in the school the chances of exposure and spread are great.

TABLE 1.—Number of Cases and Total Days Lost

Cause	1919-1920		1920-1921		1921-1922	
	Cases	Days	Cases	Days	Cases	Days
Coryza	49	213	49	234	140	760
Tonsillitis	62	327	50	246	102	728
Pharyngitis	41	181	44	209	88	620
Bronchitis	25	189	23	138	31	227
Laryngitis	2	10	2	11	2	11
Grip	121	1,038	4	85	23	157
Pneumonia	1	24	1	13	1	15
Otitis media	16	172	19	171	38	306
Sinusitis	7	87	2	7	12	73
Headache	41	124	18	73	20	45
Indigestion	37	79	63	188	60	183
Constipation	..	..	4	8	8	22
Enteritis	1	3	5	8	5	14
Fatigue	11	28	8	34	13	35
Scarlet fever	13	454	2	67	1	31
Measles	34	566	..	...	..	..
German measles	1	12	..	...	..	..
Chickenpox	..	..	39	595	1	11
Mumps	..	..	19	354	1	14
Pertussis	..	..	15	86	1	21
Conjunctivitis	1	1	69	273	10	33
Adenitis	7	54	3	32	8	41
Dermatitis	1	5	..	...	4	20
Arthritis	1	5	..	...	1	10
Accidents	38	97	41	172	37	103
Observation	16	53	..	...	8	8
Miscellaneous	85	320	52	212	59	243

In the winter of 1919-1920, there was one case of rubella with no cases following. This term began January 17, and the patient came to the infirmary March 20. April 30, seven days after the beginning of the spring term, a case of scarlet fever and a case of measles were admitted, each undoubtedly brought back from vacation. Each of these resulted in an epidemic. There were thirteen cases of scarlet fever and thirty-four of measles.

The epidemic of chickenpox, the following year, began February 4, twenty-four days after the opening of school following the Christmas holidays. The epidemic of whooping cough calls attention to an error in the statistics. No record has been kept of the number of days lost by boys who went home on account of sickness. It is very evident that fifteen cases of whooping cough would make a total of more than eighty-six days' absence. This small number is due to the fact that some boys went home as soon as a cough developed. The error, as noted in the case of pertussis, is not, however, a large one.

There were two cases of scarlet fever in this year, both occurring in the spring term. The first case entered the infirmary May 17, exactly five weeks after the opening of school, and it was impossible to find any exposure to any other case. May 23, another case occurred in a boy who, as far as could be determined, had not been in contact with the first patient. He lived in a different dormitory, went to a different dining hall, and was not associated in class room or athletic field.

During the year 1921-1922, one case each of chickenpox, scarlet fever, whooping cough, and mumps developed, all of them occurring in the spring term. This term began April 5. The case of rubella was admitted April 7; the case of mumps, April 26; chickenpox, May 20, and scarlet fever, May 23. In the last two, the incubation period was passed, and no source of contagion could be found.

The miscellaneous group includes a number of conditions which occurred infrequently or were unimportant from a health standpoint. This group contained in 1919-1920 a case of myositis ossificans, one of endocarditis, one operation for appendicitis, one case of eczema, one of sunburn, two cases of boils, two of catarrhal jaundice, and several cases of "abdominal pain." The last named were indefinite conditions, and possibly should be called indigestion. The miscellaneous group in the other years is similar.

In view of the fact that some of these conditions are allied and sometimes difficult of accurate differential diagnosis, a much better grouping would be that found in Table 2, under the headings "Respiratory Tract Infections," "Contagious" "Gastro-Intestinal" and "Miscellaneous."

The data presented in Table 2 are expressed graphically in Table 3, which is similar to the one given by Dr. Mason [2] in his studies at the Lincoln School.

Tables 2 and 3 show that respiratory tract infections were the chief cause of sickness, the contagious diseases being next. This condition was, however, reversed in 1920-1921. The studies at Lincoln School revealed a similar situation. Dr. Richard Smith,[3] in a study at River's School, Brookline, Mass., also demonstrated that the respiratory infections were the chief cause of loss of time, although the minor illnesses caused more absences than the contagious diseases. The percentage of days lost from all causes at River's School was 9.6. At the Lincoln

---

[2] Mason, H. H.: Some Records Regarding Absences and Their Causes in the Lincoln School of Teachers College, Am. J. Dis. Child. **22**:500 (Nov.) 1921.

[3] Smith, R. M.: Health Study of a Boys' School, Am. J. Dis. Child. **18**:246 (Oct.) 1919.

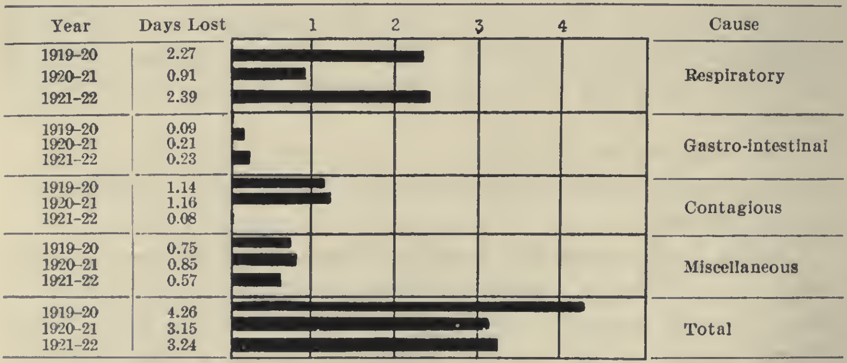
School the percentage dropped in four consecutive years from 14.9 to 8.6. It is probably not fair to compare these studies too closely, the other two being made in day schools, whereas St. Paul's is a boarding school. It is interesting, however, to note the similarity in the studies, and that in all three studies the respiratory tract infections were the chief cause of loss of time.

TABLE 2.—Amount of Time Lost as a Result of Various Causes

Cause	Amount of Time Lost								
	1919-1920			1920-1921			1921-1922		
	Cases	Days	%	Cases	Days	%	Cases	Days	%
Respiratory infections	282	2,060	2.27	150	855	0.91	349	2,277	2.39
Gastro-intestinal	38	82	0.09	72	204	0.21	73	219	0.23
Contagious	48	1,032	1.14	75	1,102	1.16	4	77	0.08
Miscellaneous	201	687	0.75	191	796	0.85	160	539	0.57
Total	570	3,861	4.26	488	2,957	3.15	586	3,112	3.24
Total possible attendance	90,440			93,852			95,274		

TABLE 3.—Percentage of Time Lost from Various Causes

	1919-20	1920-21	1921-22
Total possible attendance (days)	90,440	93,852	95,274
Total days lost	3,861	2,957	3,112
Days lost, respiratory (per cent.)	2.27	0.91	2.39
Days lost, gastro-intestinal (per cent.)	0.09	0.21	0.23
Days lost, contagious (per cent.)	1.14	1.16	0.08
Days lost, miscellaneous (per cent.)	0.75	0.85	0.57
Total days lost (per cent.)	4.26	3.15	3.24



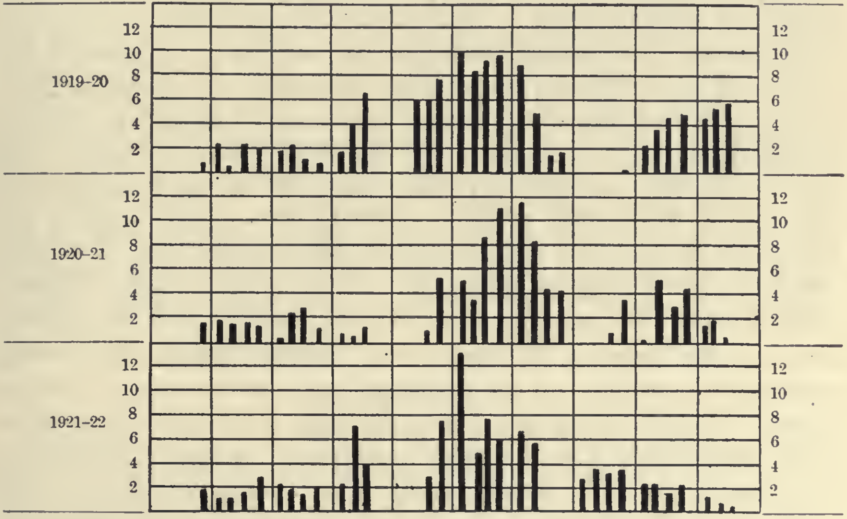
Year	Days Lost	Cause
1919-20	2.27	Respiratory
1920-21	0.91	
1921-22	2.39	
1919-20	0.09	Gastro-intestinal
1920-21	0.21	
1921-22	0.23	
1919-20	1.14	Contagious
1920-21	1.16	
1921-22	0.08	
1919-20	0.75	Miscellaneous
1920-21	0.85	
1921-22	0.57	
1919-20	4.26	Total
1920-21	3.15	
1921-22	3.24	

Table 4 shows the percentage of absences month by month and week by week. In calculating the figures for this table, the number of boys in attendance each day was used, a boy who went home was considered as being dropped temporarily. In order to check the accuracy of these figures, the total enrolment was used, and in no case was the difference in them more than one tenth of 1 per cent., so that the error caused by boys who went home is slight, and the figures given are quite accurate.

Table 4 shows at a glance the marked increase in sickness during the winter term, and, except in 1920-1921, a noticeable increase with the onset of cold weather at the end of the fall term. This high rate has been due largely to the respiratory tract infections. In February, 1920, the high rate was due almost entirely to this cause, there being 1,118 days lost, of which only fifty were lost from the other causes.

TABLE 4.—Percentage of Time Lost, Month by Month and Week by Week

	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	March	April	May	June	Average
1919-20	0.7	2.3 0.4 2.3 2.0	1.9 2.3 1.3 0.9	1.8 4.0 6.5	6.0 6.0 7.9	10.0 8.3 9.3 9.9	8.9 4.9 1.5 1.6	0.06	2.3 3.8 4.4 4.8	4.5 5.4 4.9	4.2
1920-21	1.7	1.8 1.4 1.7 1.4	0.3 2.1 2.6 1.1	0.8 0.5 1.3	1.1 5.4	5.2 3.8 8.6 11.0	11.6 8.1 4.3 4.1	0.69 3.5	0.6 5.1 3.0 4.3	1.5 1.8 0.43	3.15
1921-22	1.8	1.0 1.0 1.4 2.7	2.2 1.8 1.4 2.0	2.1 7.0 4.0	3.0 7.5	13.0 4.9 7.8 6.0	6.8 5.8	2.8 3.4 3.2 3.3	2.3 2.3 1.7 2.2	1.3 0.7 0.3	3.24



The increase during the winter of 1920-1921 was due partly to an epidemic of conjunctivitis and chickenpox; but in 1921-1922 it was due almost wholly to respiratory infections. During the first week in February (the highest point in the three years), there were fifty-eight cases admitted to the infirmary, all but five of them being cases of infection of the respiratory tract.

A study of this kind shows at a glance the chief causes of sickness, and indicates also where the chief emphasis must be placed in an attempt to reduce the rate of sickness. It would be a great help to those engaged in this kind of work if further studies, particularly in the same type of school, were available.

THE SALIVA OF THE NURSLING *

A. HYMANSON, M.D., AND HEINRICH DAVIDSOHN, M.D.
NEW YORK BERLIN

Investigations of the saliva of the nursling deserve attention from both the scientific and the clinical points of view. Saliva is readily obtained for experiment in the pure state, and a knowledge of its properties is valuable in reaching conclusions concerning the digestive fluids in general. The importance of saliva in gastric digestion is greater than has heretofore been assumed.

We have studied the saliva of the nursling under both physiologic and pathologic conditions. Before describing our experiments and conclusions, something should be said of the present knowledge of the subject. The reaction of the saliva of nurslings is normally alkaline to litmus, but nearly neutral in electrometric measurements. Reports in the literature of alterations from hour to hour, and in relation to the requirements of digestion show much discrepancy. In certain more or less pathologic states the reaction becomes acid, including ordinary decomposition in the contents of the mouth in healthy subjects. The quantity of saliva secreted in twenty-four hours is (up to 2,000 c.c.) in excess of the quantity of urine secreted. Mastication, some of the constituents of the food and condiments stimulate the flow, as do also stomatitis, the cutting of teeth, etc. The so-called albumin glands, which comprise the parotids, must be distinguished from the mucous glands, in the secretion of which mucin replaces albumin, these being represented essentially by the sublingual and small scattered mucous glands. The albumin glands secrete diastase, the production of which is not much affected by pathologic conditions. In regard to innervation, stimulation of the cranial nerves causes an abundant flow of thin saliva, while stimulation of the cervical sympathetic nerve causes an increased secretion of mucus. Reflex irritation of the buccal mucous membrane, acting through a reflex center in the medulla, may also modify both the amount and composition of the saliva. This center is connected directly with the cerebral cortex.

The saliva of the nursling is quite a modern subject for investigation compared with saliva in general, the study of which was undertaken by Simon in 1842 and Wright in 1844. The reaction of the

---

* Received for publication Feb. 20, 1923.

* From the Orphans' and Children's Asylum of the City of Berlin, Director, Prof. L. F. Meyer, M.D.

saliva at birth is a subject concerning which there have been conflicting statements, dependent, no doubt, on the use of different indicators. If the mouth is first irrigated to rid the cavity of extraneous matter, the reaction is said to be alkaline, or at most neutral—never acid. By the electrometric method the reaction appears to be approximately neutral, but not absolutely neutral, being either slightly acid or slightly alkaline.

It was once denied by several pediatricians that the new-born baby secreted any saliva, and again it was asserted that the salivary glands could function in utero. But it is now generally held that at, and after, birth, a small quantity of saliva is secreted up to about 6 weeks. After that period there is a steady increase, and at from 3 to 4 months a considerable quantity can be collected for experiment. Later the cutting of the first teeth appears to cause a considerable increase, the saliva dribbling continuously.

The presence of saliva in the early weeks of life does not imply that it is a digestive secretion at that period, and it has been denied that ptyalin is present until after the first 6 weeks. This statement is probably untrue, for a number of independent investigators have found enzyme present at birth. Moll found enzyme in a 7 months fetus, while Ibrahim discovered it in all three of the large salivary glands in 8 and 9 month fetuses. It has been shown that the proportion of enzyme increases during the first year, while after that period there is no further increase. The saliva of a child, aged 1 year, does not, in other words, differ from that of an adult. Finzi has shown that up to the age of 6 months the starch content of the food does not exert any influence on the diastatic strength of the saliva. Later the results in this province are conflicting.

EXPERIMENTAL RESULTS

Reaction.—We have made more than 100 determinations on fifty-five nurslings. In all cases the saliva was collected by aspiration during a period of fifteen minutes. The aim of the research was to establish standard values for the normal nursling. The method was this: A flexible metal aspirator, perforated with four circular openings, each about one-tenth centimeter in diameter, was used, as dentists use it, in both cheek pockets, being moved to and fro, while suction was employed with a syringe of 100 c.c. capacity. The aspirated saliva was collected in a graduated measuring glass. The interval of fifteen minutes was prolonged if the saliva was slow in accumulating. In the latter case the accumulation of the first fifteen minutes was recorded.

The amount of saliva thus obtained was read and recorded, and the reaction was first taken with a one-color indicator, usually metanitrophenol. If the test fluid was turbid, it was controlled with an indifferent fluid of the same turbidity. The content of ferment was determined by the Michaelis-Pechstein[1] method. Four Erlenmeyer flasks were filled with the following solution:

5 c.c. Kahlbaum's 1 per cent. soluble starch
20 c.c. sodium chlorid solution, fiftieth normal
3 c.c. of ⅓ primary phosphate[2]
0.30 c.c. ⅓ secondary phosphate[3]
5.7 s.c. water.

The sodium chlorid is added because salivary diastase is entirely inactive in the absence of salts. The latter can combine with all possible salts to form double combinations, each of which has characteristic peculiarities. The diastatic activity depends on the affinity of the salts for the diastase, i. e., on the completeness of the union, and on the extent of the activity on starch. The addition of sodium chlorid prevents errors in consequence of fluctuations in saline content of the saliva and guarantees the preparation of a favorable and always uniform combination of the diastase.

The necessity for the addition of the phosphate solutions arises from the fact that the reaction must be established in all ferment studies. To each of the four flasks containing the starch mixture is added 1 c.c. of saliva. In the first there is no dilution; in the second the dilution is 1 part of saliva to 1 part of water; in the third, 1 part of saliva to 3 parts of water, and in the fourth, 1 part of saliva to 7 parts of water. The duration of the test was twenty minutes at room temperature. The diastatic action was interrupted by the addition of 20 c.c. of a hundredth normal solution of iodin, when by complete hydrolysis of the starch the solution became light yellow, in other words it was colored only by the iodin. If partially red, from the presence of erythrodextrin, the cleavage is incomplete, while if the color is a deep blue the starch is not yet affected by the presence of the ferment. For the estimation of the ferment content the amounts of saliva were ascertained, in which, under conditions already described, complete cleavage of starch appears, or, in other words, until the red color is no longer in evidence. If 1 c.c. of undiluted starch is necessary, the ferment content is valued at 100. If 1 c.c. had been diluted to make 5 c.c., with complete cleavage, the valuation would be 500.

---

1. Michaelis, L., and Pechstein, H.: Biochem. Ztschr. **59**:77, 1914.

2. The formula for ⅓ primary phosphate is: 100 c.c. of a 10 per cent. solution of sodium hydroxid; 100 c.c. of a 10 per cent. solution of phosphoric acid, and 100 c.c. of water. Of this solution 3 c.c. is put in each flask.

3. The formula for ⅓ secondary phosphate is: 200 c.c. of 10 per cent. solution of sodium hydroxid and 100 c.c. of 10 per cent. solution of phosphoric acid. Of this solution 0.3 c.c. is put in each flask.

RESULTS

The reactions obtained in our experiments were strikingly constant. There were never more alkaline values than $p_H = 7.8$, or more acid values than $p_H = 6.8$. The highest acid values were found in a few tests in which the amount, having been too small for testing, had been diluted with water from fourfold to sixteenfold. The least dilute, from one and one-half to threefold, showed a p_H varying from 7 to 7.8. Electrometric controls with saliva diluted from 1:2 to 1:4 showed practically absolute agreement with colorimetrically obtained values. It is probable that the slight variations in reaction were really less than they seemed. That the alkaline value of $p_H = 7.8$ was obtained only by the colorimetric method in consequence of a defect in the indicators is hardly to be assumed. Therefore, the concentration of the saliva seems to have been too slight. Probably, however, the most acid value ($p_H = 6.8$) is too high, for it was found only in strong dilution with distilled water, with a p_H of about 6.7. With the slight concentration of the buffer salts in the saliva, with fourfold and stronger dilution, the native reaction of the saliva would be suppressed by the reaction of the water. In the future, attention must be paid to this circumstance, and, through the employment of freshly boiled water, it may be readily met. Hence in our experiments the reaction of the saliva in the nursling varies between 6.8 and 7.8 p_H and probably between 7 and 7.8. With this slight variability it is unlikely that any relationship can be found between p_H and the time of day, ingestion of food or condition of the child. Such studies, moreover, have to be opposed to technical difficulties. The very cases in which change of reaction is soonest to be expected would be in the very young and very sick nursling, in whom there is so little saliva produced that dilution would lead to errors.

As a result of our experiments we are able to establish the following facts: The saliva of the nursling, under normal and pathologic conditions, varies between slightly alkaline and neutral. Our results, therefore, deviate but slightly from those of Allaria,[4] while there is complete agreement with the latter in regard to independence of the reaction to the condition of the child. The reaction of the saliva is a function of its content of carbon dioxid and alkaline carbonate; it is proportional to the concentration of both. In theory we may assume that more alkaline values could be obtained if special measures were not taken to prevent the loss of carbon dioxid.

---

[4] Allaria, G. B.: Die chemische Reaktion des Säuglingsspeichels, Monatschr. f. Kinderh. **10**:179, 1911; Ueber die Wirkung des Speichels im Anfangsstadium der Verdauung beim Säugling, Jahrb. f. Kinderh. **74**:252, 1911.

In order to prevent the loss of carbon dioxid Bloomfield and Huck recommended that the saliva be collected under a stratum of oil. According to Starr[5] the increase of alkalescence which results from the loss of carbon dioxid amounts to 0.20 p_H. In our own investigations precautions of this sort were not taken because, with the syringe method of collecting the saliva, the carbon dioxid loss was unavoidable. This slight error in any case is not sufficient to prejudice our results.

The reaction of the saliva is, according to our measurements, but little different from that of the blood, which is normally between 7.3 and 7.5. This is readily understood, for undoubtedly the alkaline carbonate of the saliva as well as the carbon dioxid are derived from the same ingredients of the blood. Starr has even shown a proportional relation of p_H in the saliva of the adult and the carbon dioxid of the alveolar air. Is the reaction of the saliva in the nursling identical with that of the adult? It is difficult to answer this question because the findings in the adult show such lack of harmony. The authors, as Michaelis and Pechstein,[1] were unable to find any differences worth mentioning, but Starr[5] has found higher acid values in the adult, although only with an uncontrolled colorimetric method.

The constancy of the reaction of the saliva is noteworthy. In the urine and gastric juice the acidity shows great fluctuations, as this is inevitable for the maintenance of the constancy of the reaction of blood. Such fluctuations are, therefore, a criterion of renal sufficiency. Fluctuations in the acidity of the stomach contents are due chiefly to alterations in the amount of gastric juice secreted. What is then the explanation of the constancy of the salivary reaction? The answer which first suggests itself is that a certain reaction is necessary to activate the salivary ferment. According to Michaelis and Pechstein, the optimum reaction for the diastase is $p_H = 6.7$. It is true that the food soon enters the stomach and that salivary digestion largely takes place there.

Amount of Saliva.—For the normal nursling at the age of from 1½ to 3 months the amount of saliva collected during the fifteen minute intervals varied from 1.3 to 2.2 c.c., or an average of 1.6 c.c. In older nurslings, say from 5 to 8½ months of age, the amounts for the same time intervals varied from 2.5 to 8 c.c., with an average of 4.8 c.c. In the sick nursling the first to be studied were the victims of mild infections, in which cases twelve investigations were made. Only three times was an alteration found beyond the likelihood of error.

---

[5] Starr, H. E.: Studies of Human Mixed Saliva: I. The Determination of the Hydrogen Ion Concentration of Human Mixed Saliva, J. Biol. Chem. **54**:43 (Sept.) 1922; Studies of Human Mixed Saliva: II. Variations in the Hydrogen Ion Concentration of Human Mixed Saliva, ibid. **54**:55 (Sept.) 1922.

Two of these infants had whooping cough with bronchitis, and in each of them the figure was 1.5 c.c., the age being 6½ months. The third subject, a child 5 months old, with glossitis, showed an increase of a pronounced character, 10 c.c.

Sixteen nurslings with severe infection were next studied, and in all but one a considerable alteration was found. The exception was an infant, aged 2½ months, the ailment being bronchitis and the amount of saliva 1.6 c.c. In some other cases reduction of amount was so great that no saliva could be obtained, as in two children, 1 month old, with influenza. In two others, aged, respectively, 6 and 7½ months, with severe toxi-infectious processes, the amount collected was, respectively, but 0.2 and 0.4 c.c. Finally, in a child aged 6 months, with bronchopneumonia and pyelitis, the amount was 1 c.c. Eleven nurslings with acute disturbance of nutrition were then studied. During and just after the acme, there was a considerable diminution in the quantity; but afterward, say three weeks later, this had regained the normal limits. One infant, aged 1 month, with acute indigestion had no saliva at all; one of 5 months showed 0.7 c.c.; a third, aged 11½ months, had 1.5 c.c. eight days after treatment with withdrawal; a 5 months' nursling with acute indigestion showed 2.5 c.c. although in a parallel case after fourteen days the amount was but 1 c.c., and finally in a child, aged 1 year, two and one-half weeks after withdrawal treatment, the amount was 2 c.c.

In chronic disturbances of nutrition nineteen investigations were made and a distinct diminution of the amount of saliva noted. As a rule this was less pronounced than in the acute cases and in the severe infections. The diminution was more marked in the infants who were severely affected than in the mild cases. Thus, in an atrophic nursling, aged 2 months, the amount was 0.6 c.c.; in a 5 months' old dystrophic child, it was 1 c.c., and in a 10 months' old child, 2 c.c.

Diastase.—In regard to the salivary diastase young normal nurslings of ages ranging from 1½ to 3 months (ten investigations), the majority showed a ferment strength of between 300 and 600. One case each fell above and below these limits. Thus a 1½ months' old healthy nursling showed as high as 1,200, while in a sound 2 months' old child the very low figure of 50 was reached. The average was 475.

In older healthy nurslings, with age limits of 5 to 8½ months (twenty-one investigations), the ferment content was higher, usually between 600 and 1,600. In this series also there were two exceptions. In one child, aged 6½ months, the low figure of 100 was present, while at the other extreme the 8½ months' old infant gave the figure 4,800. The average of the series was 1,200. Hence there is a not inconsiderable difference in ferment strength in both older and younger nurslings, which may be set down rather to difference in the number of glands than to a greater or less amount of saliva, this being easily excluded by measuring the latter.

In regard to the amount of diastase in diseased nurslings, a study of twelve infants with mild infections showed that in but one was there a departure from the customary. In a child, aged 2 months, with an added diarrhea, the ferment strength was but 25.

Of fourteen examinations of severely infected infants, six gave positive results which were outside the possibilities of error, in which the normal ferment strength was diminished. Usually these cases occurred in the older nurslings with severe toxi-infectious disease; for example, in two of them the low figure of 50 was reached. In this series reduced ferment strength coincided with reduced quantity. In two patients failure to obtain any saliva naturally prevented making the test for ferment strength.

In acute disturbances of nutrition (eleven investigations) one nursling was without any saliva for examination. Of the others, two, aged 5 months and 11½ months, respectively, with acute dyspepsia, showed no reduction of ferment strength despite reduction in amount. The same may be said of most of the remainder. In but one case, that of a 2 months' old nursling tested two weeks after an acute attack, the ferment strength was reduced to 50. In this series convalescence was evidently more or less advanced at the time of examination. Generally speaking, this series, which was really too small for conclusions, exhibited reduced amount without reduction of ferment strength. Further studies of the quality of the saliva in these patients are already under way.

Nineteen nurslings with chronic disorders of nutrition were studied, and of this number seven, or about two-fifths, showed an undoubted diminution of ferment content, usually about 50. In five cases this was associated with diminution of quantity of saliva. In two the latter was within normal limits. Of the remainder, twelve in number, eight showed normal ferment content with diminished quantity.

SUMMARY

Active saliva occurs in the youngest nurslings tested (1 month old). Both the amount of saliva and the ferment concentration tend to increase with age, the quantity showing less range of fluctuation than the ferment content. In the disease conditions studied, the amount was more frequently and more intensively affected than the ferment content. Alteration in amount save in a single case of stomatitis was always in the direction of diminution. The coincidence of small amounts with normal ferment content was more common than that

of normal amount with lessened ferment content. In mild infections diminution of quantity was seen only in individual cases, but in severe infection that notably prejudices the organism — pneumonia, severe pyelitis—this diminution is almost constant. This is true alike of both acute and chronic infections. Chronic disturbances of nutrition affect the organism in this respect as do severe infections, while in acute types of the same disorders, only isolated examples of diminished quantity are encountered. In the chronic forms, both quantity and ferment content show diminution, while in the acute it is the amount rather than ferment content which is reduced.

There is a relative independence in the amount of saliva and ferment content, which as already stated, may be best explained by postulating a difference in the number of individual glands for each subject with the addition of a complicated nervous mechanism. In acute febrile conditions, however, the loss of water by the skin could in theory reduce the amount of saliva.

A BACTERIOLOGIC STUDY OF ACUTE DIARRHEAS IN YOUNG CHILDREN*

MARTHA WOLLSTEIN, M.D.
NEW YORK

Among infants there is a distinct seasonal incidence of disease. At the Babies' Hospital, to which contagious diseases are not admitted, the character or type of the ward cases varies with the seasons, although the quantity (numbers and severity) varies from year to year. Thus, for example, the number of cases of pneumonia increases from early fall until late winter, to be followed by empyema and then in the early spring by tuberculosis. The late spring is a hang over season for tuberculosis and empyema, and in the early summer the intestinal diseases begin to appear. There are few of these in June; they increase in number through July and August, and diminish after the middle of September. Frequently, however, the severest intestinal lesions are found at necropsy in October, among children whose illness has lasted five or six weeks or who give a history of mild diarrhea earlier in the summer. By November the ward for intestinal diseases is practically empty, and pneumonias have reappeared. Of course, there are cases of respiratory infection in summer and intestinal infection in winter, but the great majority of these appear in their proper season. It has been noted during the last few years that the cases of intestinal disease which come to necropsy present less severe lesions than were found ten or fifteen years ago. Since no bacteriologic study of the summer cases had been made for some time, a systematic study during the summer of 1922 was undertaken.

A ward was set aside for patients with infectious diarrhea, and special nurses were put in charge. All possible danger of carrying infection to the other wards was guarded against by precautions which were observed by the nurses and physicians entering this ward, and by special care given the linen and utensils used by the children. Diapers were made of gauze and were destroyed by burning.

The study was continued from June 5 to September 15. One hundred and thirteen bacteriologic examinations were made on eighty-six children; twenty-five were studied twice and two were examined

---

* Received for publication Feb. 20, 1923.

* From the Babies' Hospital of the City of New York.

* Read before the New York State Association of Public Health Laboratories, Albany, N. Y., Nov. 1, 1922.

three times. In addition, postmortem intestinal cultures were made in ten cases. The patients ranged from 6 weeks to 4 years of age. Sixty-eight were less than 1 year old, and only three were more than 3 years of age.

TECHNIC

Specimens of intestinal contents for bacteriologic examination were obtained with the proctoscope and a long sterile swab. Occasionally a child was too ill to be carried to the dressing room for examination. In such cases a sterile tube was introduced into the rectum and a specimen obtained without disturbing the patient. The proctoscope used at the hospital has been described by Drs. Spence and McLean.[1] The instrument is introduced to a distance of 6 inches without difficulty, and with no pain to the child, even the youngest. The mucosa of the rectum and lower sigmoid can be seen and the following points noted: the color of the intestinal lining; its appearance, whether smooth or granular; the amount of mucus; the bleeding points; the presence or absence of ulcers; the character of the bowel contents, and the presence or absence of tenesmus. A long sterile swab is introduced through the proctoscope, and the material obtained directly from the rectal mucosa is plated immediately on Endo plates. Kligler's [2] modification of this medium, using less of the sulphite-fuchsin mixture, 0.5 instead of 1.0 c.c., was employed.

From this point on our technic followed closely the directions laid down in the circular on diagnostic examinations issued by the New York State Board of Health,[3] a copy of which had been kindly furnished by Miss Kirkbride. All gram-negative, nonmotile, non-gas forming bacilli which agglutinated with polyvalent antidysentery serum were studied further in the following sugars, using the Andrade indicator: dextrose, lactose, mannite, maltose, saccharose and dulcite. The fermentation of mannite served to differentiate the Shiga bacillus from the Flexner group, and the fermentation of maltose served to differentiate the so-called Flexner from the Mount Dessert strains within the group of mannite fermenters. A few strains fermented saccharose. We found this differentiation at least as clear cut as that obtained by means of the five serums of the Murray subgroups V, W, X, Y and Z.

Finally, agglutinations were made with the three (Shiga, Flexner and Mount Dessert) specific antidysentery rabbit serums furnished by the New York State Laboratory, and the type of bacillus determined.

---

[1] Spence, R. C., and McLean, S.: Method of Obtaining Direct Cultures from Intestinal Ulcers in Infants and Young Children, J. A. M. A. **75**:742 (Sept. 11) 1920.

[2] Kligler, I. J.: J. Exper. Med. **28**:319 (Sept.) 1918.

[3] New York State Department of Health, Form 18, 1921.

Further agglutination studies with all the mannite fermenting cultures were made in the serums of the subgroups V, W, X, Y and Z.

The intestinal cultures from twenty of the eighty-six children, when examined for dysentery bacilli, gave positive results. The cultures from three children showed the presence of the Shiga type of bacillus; five showed the Flexner type, and twelve the Mt. Dessert type. These groups will be discussed separately. Of the eighty-six children, thirty-two were clinically diagnosed as not having dysentery. Therefore, while 20⅓ per cent. of all cases examined were positive for *B. dysenteriae,* 37 per cent. of the cases presenting the clinical symptoms of dysentery were positive.

Infection with Shiga Type of Dysentery Bacillus (Three Cases).—In this country, infection with the Shiga bacillus is rare, and the group is the smallest in our series. The three patients harboring this type of dysentery organism were 5 months, 6 months and 2 years old, respectively. The youngest infant in the group left the hospital against advice, unimproved. The eldest of the three children died after an illness of four weeks. On proctoscopic examination during life, several ulcers were seen in the upper part of the rectum, and at necropsy one week later an ulcerative and pseudomembranous colitis was found. The third child of this group, who was 6 months old, recovered after an illness of two weeks' duration and of moderate severity. Her intestinal mucosa, seen through the proctoscope on the sixth day of illness, was deeply congested, covered with glairy mucus and showed many capillary bleeding points. The dysentery bacilli were no longer present in the stool one week after the first positive examination.

All three of these patients were treated with antidysentery serum made by the New York State Board of Health.

Infection with Flexner Type of Dysentery Bacillus (Five Cases).—This group was composed of three infants less than 1 year old, and two children who were 2 years of age. Two of the patients recovered, 11 months and 2 years of age, respectively; two died, and one left the hospital against advice, in an unimproved condition. Ulcers were seen through the proctoscope in the intestinal lining of one of the children. Two others showed deep congestion with bleeding from many points around swollen follicles, and two were too ill to be examined.

The illness of the five children in this second group lasted from five days to two weeks. Blood was present at some time in the stools of all five. Serum therapy was administered to the entire group.

Infection with Mount Dessert Type of Dysentery Bacillus (Twelve Cases).—The twelve children comprising this, the largest of our groups, were between 3 months and 4 years of age. Four of them recovered;

two improved; five died and one was removed against advice, unimproved. Nine patients were examined with the proctoscope. Ulcers were seen in four cases. In four others the rectal mucosa was congested and bleeding. In one a normal intestine was demonstrated. This little girl, 11 months old, had a mild diarrhea and was but slightly ill. The stools never contained blood, and clinically her case was not classed as dysentery. The positive laboratory findings came as a surprise.

It should be noted that blood in the stools does not necessarily mean ulceration of the intestine. The intensely congested mucosa bleeds readily even when no loss of substance has occurred.

The fatalities in this group occurred after an illness of from four to six weeks, while recovery took place after from two to three weeks. Serum was administered to all the children in this group that recovered, to one child that improved and to three of the five children that died.

The patients that are removed from the hospital in an unimproved condition are practically always hopelessly ill, and the parents' plea that "the child be allowed to die at home" cannot be denied. Therefore, such cases must be classed with those that died. It will be noted that, as is usual, the Shiga group of dysentery infections was accompanied by the highest number of fatalities, 66⅔ per cent. The Flexner group had a mortality of 60 per cent., and in the Mount Dessert group 50 per cent. of the patients died.

Ulceration occurred in 33½ per cent. of the Shiga and Mount Dessert types of infection and in 20 per cent. of the Flexner type. The severest and most extensive intestinal lesions and the longest course were found among the Mount Dessert group.

To sum up, while Shiga bacillus infection was accompanied by a higher mortality rate than was either of the mannite fermenting types of dysentery bacillus, it seemed to run a slightly shorter course. This is in keeping with the comparatively rapid disappearance of Shiga bacilli from the stool as noted by several observers.[4] Prolonged illness, longer than four weeks in duration, was more frequent in the mannite fermenting types of dysentery infections; and such prolonged cases were accompanied by severe and extensive intestinal lesions. These lesions were pseudomembranous and ulcerative in type, involving all of the large intestine and the last 30 cm. of the ileum. In our experience such an extensive necrotic lesion does not occur early in the disease.

SERUM TREATMENT

Antidysentery serum was administered to seventeen of the twenty children infected with the dysentery bacillus. Seven recovered; six died; one improved, and three were removed from the hospital before the treatment was completed. The serum was administered intramuscularly in most cases, subcutaneously in some, and intravenously in one instance to a very sick child. Four doses of 20 c.c. each were usually given. The immediate effect of the serum was not remarkable, in that neither the fever nor the toxic symptoms were acutely influenced. No child treated without serum recovered, but one such patient improved. The serum treatment was begun on the third to the sixth day of the illness of the seven children who recovered, and on the fourth day in the case of the child who improved before she was removed from the hospital. In three of the fatal cases serum treatment was begun on the first, third and fourth days of the disease, and in the other three it was delayed until the seventh and fifteenth days. The children who left the hospital against advice were treated with antidysentery serum on the first and second days and in the third week of the attack of dysentery. It may be said, then, that while the administration of antidysentery serum in the first days of the disease does not always effect a cure, its delay until the second week is fatal. In other words, while eight of thirteen children to whom the serum was given, on or before the sixth day of an attack of dysentery, recovered, four children who received the serum later than the seventh day died. The series is a small one, with suggestive but not decisive results.

---

[4] Mackie, F. P., and Trasler, G.: Indian M. Gaz. **57**:85 (March) 1922.

The total death rate for the twenty dysentery cases was 40 per cent. Adding the unimproved cases of patients who undoubtedly died to the known deaths, 55 per cent. of the patients in the series died, and 45 per cent. recovered. Bernstein, Kling and Rosenblatt,[5] from their experience in the Vienna epidemic of 1920, state that serum therapy of dysentery patients does not prevent the development of the chronic stage of the disease, nor influence the severely toxic cases. Lantin,[6] from his experience with dysentery in the Philippines, believes that without serum therapy the mortality rate is increased. Josephs and Davison[7] noted no difference in the course or mortality rate among twenty children treated with antidysentery serum.

It was planned to examine the stool before discharging the children, in order that no positive carrier should be sent out of the hospital. Dysentery bacilli had disappeared on the seventh, eighth, tenth and eleventh days of the illness, in four cases, and were still present in the stool on the thirteenth day in one instance.

---

[5] Bernstein, S., Kling, D., and Rosenblatt, S.: Wien. klin. Wchnschr. **34:** 531-549, 1921.

[6] Lantin: Philippine J. Sc. **19:**629, 1921.

[7] Josephs, H. W., and Davison, W. C.: Serotherapy of Bacillary Dysentery in Children, J. A. M. A. **77:**1863 (Dec. 10) 1921.

AGGLUTINATION REACTIONS

The sharp serologic distinction between the Shiga and the mannite fermenting types of dysentery bacilli was made very clear by agglutination reactions with the polyvalent and the specific antidysentery serums. These reactions also brought out the close relationship between the Flexner and the Mount Dessert groups of dysentery bacilli.

The three strains of Shiga bacilli isolated from children in the first group failed to agglutinate in polyvalent antidysentery serum in dilutions above 1 to 800, and in the Flexner and Mount Dessert serums in dilutions above 1 to 50. Three of the Flexner strains and four of the Mount Dessert strains were agglutinated in dilutions of 1 to 100 by the specific Shiga serum, while the reactions of all mannite fermenting strains in the polyvalent serum were high, in most cases reaching the limit of the titer (3200 or 6400). Only one strain did not agglutinate in the polyvalent serum in a dilution above 1 to 100, and its specific (Flexner) serum agglutinated this strain only in the same dilution.

AGGLUTINATION OF MURRAY SERUMS BY STRAINS OF MANNITE FERMENTING DYSENTERY BACILLI ISOLATED IN THE COURSE OF THIS STUDY

Strains	Serums								
	Polyvalent	Shiga	Flexner	Mount Dessert	V	W	X	Y	Z
Shiga (control)	3,200	6,400	100	100					
A M	800	1,600	25	50					
D H	400	3,200	0	50					
J J	400	3,200	50	50					
Flexner (control)	6,400	200	6,400	3,200	1,600	1,600	200	0	1,600
J P	100	100	100	50	200	0	0	800	200
D N	6,400	200	3,200	800	0	0	0	0	100
F W	800	100	800	200	200	1,600	100	0	200
M N	3,200	0	1,600	800	0	0	400	0	0
A T	6,400	0	3,200	800	0	100	100	0	0
Mount Dessert (control)	6,400	0	3,200	6,400	100	0	800	100	0
K F	6,400	0	3,200	6,400	400	1,600	3,200	1,600	200
H N	3,200	0	800	3,200	0	0	100	0	100
J B R	400	0	200	25	100	0	0	100	0
J B I	800	100	100	800	400	800	800	1,600	200
C A	6,400	100	1,600	3,200	0	0	200	0	0
T A	3,200	0	800	1,600	400	0	800	0	0
T F	6,400	100	800	3,200	800	800	400	1,600	1,600
J B E	6,400	0	400	6,400	800	12,800	800	800	200
M R	1,600	0	400	1,600	400	1,600	800	1,600	100
I D	6,400	0	3,200	6,400	800	3,200	200	1,600	200
V D	3,200	0	400	3,200	800	1,600	800	1,600	200
B C	6,400	100	400	6,400	400	100	800	1,600	1,600

The specific Flexner and Mount Dessert serums agglutinated strains of their homologous types, as a rule, in one to two dilutions beyond that in which the heterologous types also agglutinated.

One strain, though giving the fermentation reaction of the other Mount Dessert strains, failed to agglutinate in the Mount Dessert serum in a dilution beyond 1 to 25, while with the Flexner serum it agglutinated at 1 to 100. This strain, with the more highly specific serums of Murray,[8] agglutinated the V and Y serums in a dilution of 1 to 100. Therefore, its serologic classification was not possible. The important point, however, is that its highest agglutination reaction was obtained with the polyvalent serum used for therapeutic purposes. Its fermentation reactions placed it in the nonmaltose fermenting group of Flexner dysentery bacilli.

No sharp differentiation of the seventeen strains of mannite fermenting dysentery bacilli isolated in the course of this study was obtained with the five Murray serums V, W, X, Y and Z. As the accompanying table shows, seven of the strains agglutinated two or more of the Murray serums equally well, so that their classification into a Murray subgroup was not possible. None of the strains failed to show agglutination with the polyvalent, therapeutic serum used. Therefore, their further serologic classification can only be of academic and not of practical importance, and it is evident that the antidysentery serum made by the New York State Board of Health for therapeutic purposes contained immune bodies corresponding to the antigens of all strains of dysentery bacilli isolated from clinical cases of dysentery occurring during an average New York summer service among young children.

The children's serums were tested for agglutination on admission to the hospital in ten instances, with negative results. Since a dose of antidysentery serum was administered as soon as the infants were admitted to the dysentery ward, this part of the work had to be omitted.

It is interesting that this series of cases studied with improved technic gave a lower percentage of positive dysentery infections (20⅓ per cent.) than did a series at the Babies' Hospital in 1903,[9] when 35 per cent. of positive results were obtained. Davison's [10] high incidence of 83 per cent. of dysentery bacillus infection in cases of acute ileocolitis has never been seen at the Babies' Hospital.

While eight patients died in the present series of twenty cases, twenty-nine died (74 per cent.) in the earlier series of thirty-nine cases. Even when the three unimproved cases are added to the known fatalities, the difference between 55 and 74 per cent. is obvious.

Among the sixty-six cases found negative for dysentery bacilli by bacteriologic examination, thirty-four were clinically diagnosed as dysentery and thirty-two were not. In the latter series the stool examination was made either because diarrhea was a symptom, more or less transient, of a general condition (sepsis, pneumonia, etc.) or because

---

8. Murray, J. R.: Army M. Corps **31**:257, 1918.
9. Wollstein, Martha: J. M. Research **10**:11, 1903-1904.
10. Davison, W. C.: Bull. Johns Hopkins Hosp. **31**:225 (July) 1920; J. Exper. Med. **32**:651 (Dec.) 1920.

the case was frankly one of intestinal intoxication or noninfectious diarrhea.

In the group of clinical cases of dysentery the mortality rate was 41 per cent. In the noninfectious diarrheas it was 40⅝ per cent. Compared with 40 per cent. mortality for the proved cases of dystentery and 39⅓ per cent. mortality for the entire number of admissions for intestinal disorders, the rate of fatalities is a remarkably even one.

OTHER ORGANISMS

Most interesting were two cases of typhoid fever diagnosed by means of the stool examination. The first case was that of a boy, aged 4 months, who was admitted to the hospital because of diarrhea and vomiting of two weeks' duration. The stools contained no blood, and he was moderately prostrated. Proctoscopic examination demonstrated a mildly congested mucosa but no ulcers. Typhoid bacilli were isolated instead of the expected dysentery bacilli, and then the child's blood was found to give a positive Widal reaction in a dilution of 1 to 100. The boy died of exhaustion after an illness of six weeks, when the typhoid bacilli had disappeared from the stools.

The second child developed diarrhea after he had been in the hospital two weeks, and on the Endo plates inoculated from the specimen of blood-stained mucus obtained by proctoscopic examination many typhoid colonies grew. The child died after an illness of one week, and at necropsy the ileum showed the lymphoid swellings typical of typhoid fever in young children, without ulceration. The bacilli were readily isolated a second time from the intestinal contents obtained at necropsy. While this second typhoid infection undoubtedly occurred in the hospital, its exact source could not be traced. The two children were not on the same floor and they were attended by different nurses. Insufficiently sterilized linen may have been involved.

These two cases emphasized the difficulty encountered in making a diagnosis of typhoid fever in infancy in a nonepidemic period, and demonstrate the similarity of the clinical course of typhoid fever and infectious diarrhea at this age.

An instance of paratyphoid A infection was found in a boy, 2½ months old, admitted as a feeding case with diarrhea of three days' duration. The child recovered, but the bacilli were still present one month after admission. The original source of infection in this instance could not be found. Careful inquiry failed to show any case of illness in the child's immediate surroundings.

A strain of the Morgan group of bacilli was isolated from a child whose illness was diagnosed as dysentery. This bacillus was at first mistaken for *B. dysenteriae,* since its gas production in glucose was very feeble and it did not ferment lactose nor mannite. It was slightly motile, however, and failed to agglutinate the polyvalent dysentery serum or any of the monovalent serums.

B. faecalis alcaligenes was isolated from the stools of a 6 months old boy whose proctoscopic examination showed much mucus over a congested, bleeding mucosa. The child died, and no dysentery bacilli were found in cultures made from the intestinal mucosa at necropsy. Two strains of nonlactose fermenting intermediate bacilli which do not fit into any group were isolated and reserved for future study.

Finally, *B. pyocyaneus* was found in such large numbers in three instances that the presence of other organisms was obscured. One of these cases, at least, ran a clinical course typical of dysentery, yet two stool cultures on different days failed to show *B. dysenteriae.*

SUMMARY

Bacteriologic examinations of stools from a series of eighty-six young children admitted to the Babies' Hospital with some form of intestinal disturbance were made, and twenty children, or 23½ per cent., were found to harbor dysentery bacilli.

Among the twenty positive dysentery cases, there were three of the Shiga type of *B. dysenteriae,* five of the Flexner type and twelve of the Mount Dessert type.

The highest mortality rate occurred among the group of Shiga infections; but the group of Mount Dessert infections showed the most prolonged course and the severest lesions at necropsy.

The mortality rate of the dysentery group of cases was 40 per cent., while the mortality of the entire group was 39½ per cent.

Serum therapy was applied in seventeen of the twenty children suffering from dysentery, with no untoward, and no strikingly positive, results.

Two cases of typhoid and one of paratyphoid infection were discovered in the course of the study.

A STATISTICAL ANALYSIS OF THE CAUSES OF PALPABLE LYMPH GLANDS IN THE NEW-BORN *

LOUIS DUNN, M.D., AND HALBERT L. DUNN, M.A., M.D.
MINNEAPOLIS

The variation in the number of discernible lymph nodes in the new-born has given rise to divergent views concerning the normal occurrence. The epidermis and subcutaneous tissue of an infant are so thin and soft that a nerve or artery, a bony protuberance or tendon can readily be misinterpreted as an enlarged gland. External factors, such as coryza, infection and fever, influence the relatively unstable system of the new-born and bring about enlarged lymph nodes. Prenatal factors, such as syphilis, must also be considered. The purpose of this study is to analyze, in a carefully controlled group of cases, some of the manifold causes which give rise to the palpable glands of the new-born. We are grateful to the Asbury Hospital, Minneapolis, for cooperation in the collection of material, and we are also indebted to Drs. R. E. Scammon and W. P. Larson for their valuable suggestions.

The results of previous work done upon this subject are somewhat antagonistic. Jensen [1] published a work upon palpation of the occipital and cervical glands of the new-born during the first nine days of life. He comes to the conclusion, after a study of 240 babies, that no pathologic significance can be attached to the frequent discovery of palpable lymph nodes and that the explanation of this condition on the basis of an infection is illogical. Coerper,[2] after a study of 100 new-born infants, concluded that the swelling of the glands must be due entirely to either an infection or a physiologic activity of the lymph system. Baer [3] agrees with Coerper that the palpability of peripheral glands in the new-born signifies nothing pathologic and presupposes, therefore, no preceding sickness. He also arrives at the sensible conclusion that it is extremely difficult to distinguish between normal glands which are just palpable and moderately pathologic enlargements. He advances this explanation as a reason for the variation in the results of different

---

* Received for publication, Feb. 21, 1923.

* Contribution from Asbury Hospital, Minneapolis, and Department of Anatomy, University of Minnesota.

[1] Jensen, T.: Hintere Hals- und Nackendrüsen bei Säuglingen in den ersten neun Lebenstagen, Ztschr. f. Kinderh. **14**:176 (March 28) 1916.

[2] Coerper, C.: Ueber die Palpation peripherer Drüsen und deren klinische Bedeutung bei Kindern der ersten zwei Lebensjahre, Monatschr. f. Kinderh. **13**:458 (Oct.) 1915.

[3] Baer, A.: Zur Schwellung der peripheren Lymphdrüsen im Säuglingsalter, Jahrb. f. Kinderh. **56**:814, 1902.

investigators. Reiche,[4] and Grosser and Dessauer [5] find that a large percentage of cubital glands of infants showing signs of congenital syphilis are palpable. Gundobin,[6] in a study of fifty new-born infants, finds no palpable glands in half of his cases, while in the other half the cervical and inguinal glands appear most frequently. Stahr,[7] Dietrich,[8] Vierordt,[9] Hochsinger [10] and Hess [11] offer data bearing on the subject to a less extent. The results of these authors will be considered later in the discussion.

METHODS AND MATERIAL

The conditions for procuring the data were advantageous. The material was collected during the months of November, December and January (1920 and 1921). Considering the fact that respiratory infections start during the early winter in Minneapolis, it is surprising that more nose and throat infections did not occur. Only one case of coryza was noted in the entire series of 102 cases, and this baby was isolated until the rise in temperature and symptoms had abated. The work was carried out in the babies' ward of the Asbury Hospital. The room was kept at an average temperature of about 80 F., and extreme care was observed in aseptic handling of the babies. The infants were palpated in the morning between 8 and 9 o'clock, and the observations were made every two days. The new-born infants were palpated as soon as possible after birth, usually within the first two hours. Since it was not practical to examine the infants every day, some of the data were obtained on the first, third, fifth, seventh, ninth, eleventh and thirteenth days after birth, and the remaining were secured on the first, second, fourth, sixth, eight, tenth and twelfth days.

The babies were weighed between 8 and 10 a. m., and their rectal temperatures taken and recorded at this time. The senior investigator did the palpation for the entire series in order to eliminate differences in judgment. The baby to be examined was unclothed and placed on a table with its head toward the observer. The investigator palpated all lymph glands in two directions, at right angles to each other. First he felt for the mental and cervical glands. After identifying the presence of the cervical glands, deeper pressure was made in a search for the transverse process of the atlas, which can be mistaken for a lymph node in a malnourished infant. Passing the finger still farther posteriorly, the posterior auricular and occipital nodes were sought for in turn. The axillaries were more difficult to examine. To accomplish this the observer grasped the right arm of the baby with his right hand and palpated the right axilla with the middle finger of his left hand. In order to distinguish between an enlarged lymph node and the head of the humerus, he rotated the arm of the infant and outlined the articular surface of the head of the humerus as it glided beneath his finger. The investigator next palpated the epitrochlear and inguinal nodes. In a majority of cases the inguinal nodes were visible as well as palpable, especially if the legs of the infant were extended and slightly separated.

---

[4] Reiche, A.: Ueber den diagnostischen Wert tastbarer Cubitaldrüsen bei Säuglingen, Monatschr. f. Kinderh. **6**:511 (Oct.) 1908; abstr. Jahrb. f. Kinderh. **68**:494, 1908.

[5] Grosser, P., and Dessauer, A.: Ueber die diagnostische Bedeutung fühlbarer Kubitaldrüsen bei Kindern, München. med. Wchnschr. **58**:1130 (May 23) 1911.

[6] Gundobin, A. P.: Die Besonderheiten des Kindesalters, Berlin, 1912, p. 161.

[7] Stahr, H.: Die Zahl und Lage der submaxillaren und submentalen Lymphdrüsen vom topographischen und allgemein anatomischen Standpunkte, Arch. f. Anat. u. Physiol., December, 1898, p. 444.

[8] Dietrich: Die Palpation der Lymphdrüsen, Sitzungsb. d. phys.-med. Soc. zu Erlang. **18**:52 (July) 1886.

[9] Vierordt, H.: Daten und Tabellen für Mediziner, Ed. 3, Jena, 1906.

[10] Hochsinger, C.: Ueber tastbare Cubital- und Seitliche Thoraxlymphdrüsen im Säuglingsalter, Wien. med. Wchnschr. **57**:2114 (Oct.) 1907.

[11] Hess, A. F.: Enlargement of the Epitrochlear and Other Lymph Nodes in Infants, Arch. Pediat. **24**:602 (July) 1907.

The babies examined numbered 102; fifty-two boys and fifty girls. The series represents 102 consecutive deliveries from 1,100 babies born within a period of twelve months in the maternity department of Asbury Hospital. All the infants were Caucasian. One baby died on the first day as a result of birth trauma and instrumental delivery; another was taken out of the hospital on the second day; all the others stayed at least six days. Eleven went home on the seventh day; thirty-one more left on the ninth day, and only eight babies remained in the hospital after the thirteenth day. Any factor which might influence the number of palpable lymph glands was carefully noted. One child had a cold and temperature of 104 F. on the second day; ten were jaundiced; six had infected eyes; eighteen were circumcised; two had vaginal discharge, which, in one instance, proved to be gonorrheal in origin; twenty-five ran a temperature of more than 100 F. at some time during their sojurn in the hospital; four had infected or moist cord stumps; one showed rectal bleeding; and fifteen were premature infants, weighing between 4 and 5 pounds. The mouth, nose and pharynx were examined for discharge but not for redness of the mucous membrane or slight signs of infection.

The data collected as described above are qualitative and not quantitative. The glands were classified into three types: just discernible, distinctly palpable and swollen. The accuracy of such qualitative data, depending largely upon the judgment and sense of touch of the investigator, can, of course, be questioned since they cannot have the mathematical precision of quantitative measurements. Everything possible was done to eliminate the personal equation. The technic was exactly the same in all cases. The investigator used the same finger to palpate similar nodes and held the babies in identical positions. He knew nothing previous to the completion of the collection of data concerning the results of Coerper, Baer and Jensen in order that their conclusions might not warp his judgment.

While the accuracy of the data depends entirely upon the individual judgment and the care observed in their collection, their significance can only be determined by a qualitative statistical study. In this instance the material was reduced to a percentage basis. By means of this an accurate estimate of results was obtained. Tables were constructed of the accessory factors which might influence the enlargement of lymph glands. Others were made to give detailed data concerning the inguinal, occipital and cervical glands. None were made, however, for the axillary, cubital or mental glands, since these nodes were not palpable in any instance in the entire series. They will be considered in the discussion only.

TABLE 1.—Average Temperature and Weight

Time in Days	No. of Cases	Average Temperature, Degrees	No. of Cases	Average Weight, Pounds
1	72	98.33	99	7.306
2	29	99.06	25	6.956
3	69	98.94	66	6.945
4	24	99.07	17	6.672
5	72	98.35	72	6.993
6	26	98.08	26	6.861
7	57	98.22	56	7.071
8	16	98.36	14	7.021
9	41	98.33	42	7.093
10	12	98.12	10	6.937
11	22	98.17	19	7.181
12	2	97.30	2	7.470
13	6	98.17	6	7.542

CONSIDERATION OF TABLES

The average temperatures and weights of the babies are shown in Table 1. This table affords a check on the normality of the new-born infants under observation. The temperature taken by rectum ranged between 98 and 99 F. In only one group was the average temperature above 99 F. and this one represented twenty-four babies, three of whom had a temperature of more than 101 F. According to the normal figures of Vierordt[9] the average temperature is 100 F. at birth and 99.5 F. during the first week of postnatal life. The temperatures of these new-born infants were lower than normal, owing perhaps to the fact that birth temperatures were taken from about fifteen to twenty minutes after birth, and reflect, therefore, the heat loss resulting from the exposure of the baby. The infants were covered very lightly with only one blanket during their sojourn in the hospital which probably accounts for the slightly subnormal body temperatures.

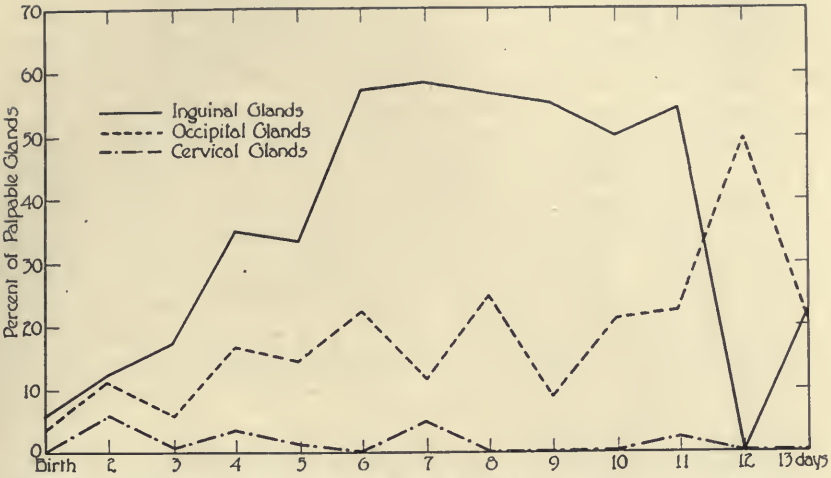


Chart 1.—Degree of palpability of the inguinal, occipital and cervical lymph nodes for each day.

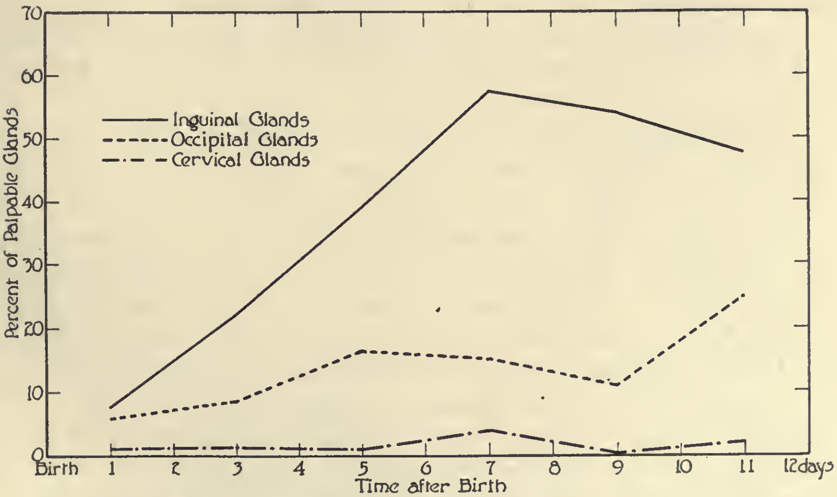


Chart 2.—Degree of palpability of the inguinal, occipital and cervical lymph nodes grouped for each two days.

The average birth weight (Table 1) was 7.3 pounds, which agrees approximately with the average new-born weights given by Emerson and Manny.[12] The postnatal weight loss also agrees with the normal, established by Hammett;[13] this loss amounts to 5 per cent. of the new-born weight on the third day, sinks to 8.6 per cent. on the fourth and then gradually recovers, becoming normal on the twelfth day.

In order to estimate the relative significance of the inguinal, occipital and cervical lymph nodes, the number of palpable glands in the respective regions was counted each day. The percentage of occurrence of palpable lymph nodes was calculated, and the results summarized in Tables 2 and 3. Table 2 shows the percentage presence or absence of these lymph nodes. Owing to insufficient data, the results are somewhat irregular, and consequently Table 3 is prepared from averages based on the same data grouped for two day periods instead of one. A graphic portrayal of the percentage of palpable lymph glands is shown in Charts 1 and 2.

The curve showing the percentage of discernible inguinal nodes (Chart 2) rises steadily from about 8 per cent. on the first day to a height of approximately 58 per cent. on the seventh day and then steadily and gradually falls to 48 per cent. on the eleventh day.

The curve based upon the palpable occipital glands ascends from 6 per cent. on the first day of life to about 16 per cent. on the fifth day, then descends slightly to 11 per cent. on the ninth day, and finally makes a sharp climb to 25 per cent. on the eleventh day.

The curve showing the percentage of cervical involvement shows no definite tendency, the number of cervical glands to be felt on any one day ranging between 0 and 4 per cent.

The percentages of palpable inguinal and occipital glands are correlated with the age of the child in days, while the percentage of swollen cervical glands shows no such correlation.

Other factors besides time influence the percentage of glands which can be palpated. The relation of body weight to discernible lymph nodes (Table 4) demonstrates that the premature infant weighing between 4 and 5 pounds has a very much higher percentage of palpable glands than the child weighing from 5 to 10 pounds. Eighty per cent. of the inguinal glands are enlarged in infants weighing from 4 to 5 pounds in contrast to about 31 per cent. in those weighing from 5 to 10 pounds; 53 per cent. of the occipital and 13 per cent. of the cervical glands in the premature infant are increased in size in contrast to approximately 11 per cent. and 1 per cent., respectively, in the heavier

---

[12] Emerson, W. R. P., and Manny, F. A.: Weight and Height in Relation to Malnutrition, Arch. Pediat. **37**:468 (Aug.) 1920.

[13] Hammett, F. S.: The Relation Between Growth Capacity and Weight at Birth, Am. J. Physiol. **45**:396 (March) 1918.

TABLE 2.—PERCENTAGE PRESENCE AND ABSENCE OF LYMPH GLANDS

Time in Days	No. of Cases	Nonpalpable Lymph Nodes									Palpable Lymph Nodes								
		Inguinal			Occipital			Cervical			Inguinal			Occipital			Cervical		
		Right	Left	Both	Right	Left	Both	Right	Left	Both	Right	Left	Both	Right	Left	Both	Right	Left	Both
1	102	93.1	95.1	94.1	94.1	98.0	96.1	100.0	100.0	100.0	6.9	4.9	5.9	5.9	2.0	3.9	0.0	0.0	0.0
2	35	85.7	88.6	87.2	85.7	91.4	88.6	94.3	97.1	95.7	14.3	11.4	12.8	14.3	8.6	11.4	5.7	2.9	4.3
3	72	82.0	83.3	82.7	93.0	95.8	94.4	99.6	100.0	99.8	18.0	16.7	17.3	7.0	4.2	5.6	1.4	0.0	0.7
4	27	59.3	70.4	64.9	81.5	85.2	83.4	96.3	96.3	96.3	40.7	29.6	35.1	18.5	14.8	16.6	3.7	3.7	3.7
5	73	64.3	68.5	66.4	83.6	85.0	84.3	97.3	100.0	98.7	35.7	31.5	33.6	16.4	12.3	14.3	2.7	0.0	1.3
6	27	44.4	40.7	42.6	77.8	77.8	77.8	100.0	100.0	100.0	55.6	59.3	57.4	22.2	22.2	22.2	0.0	0.0	0.0
7	67	37.3	46.3	41.8	86.6	89.6	88.1	94.0	95.5	94.8	62.7	53.7	58.2	13.4	10.4	11.9	6.0	4.5	5.2
8	22	40.8	45.5	43.2	72.7	77.4	75.1	100.0	100.0	100.0	59.2	54.5	56.8	27.3	22.7	25.0	0.0	0.0	0.0
9	47	40.4	49.0	44.7	91.5	91.5	91.5	100.0	100.0	100.0	59.6	51.0	55.3	8.5	8.5	8.5	0.0	0.0	0.0
10	12	50.0	50.0	50.0	75.0	83.4	79.2	100.0	100.0	100.0	50.0	50.0	50.0	25.0	16.6	20.8	0.0	0.0	0.0
11	23	43.5	47.9	45.7	82.6	73.9	78.3	95.6	100.0	97.8	56.5	52.1	54.3	17.4	26.1	21.7	4.4	0.0	2.2
12	3	100.0	100.0	100.0	33.3	66.7	50.0	100.0	100.0	100.0	0.0	0.0	0.0	66.7	33.3	50.0	0.0	0.0	0.0
13	7	71.5	85.7	78.6	85.7	71.4	78.6	100.0	100.0	100.0	28.5	14.3	21.4	14.3	28.6	21.4	0.0	0.0	0.0

TABLE 3.—PERCENTAGE PRESENCE AND ABSENCE OF LYMPH GLANDS (GROUPED)

Time in Days	No. of Cases	Nonpalpable Lymph Nodes									Palpable Lymph Nodes								
		Inguinal			Occipital			Cervical			Inguinal			Occipital			Cervical		
		Right	Left	Both	Right	Left	Both	Right	Left	Both	Right	Left	Both	Right	Left	Both	Right	Left	Both
1– 2	137	91.2	93.4	92.3	91.9	96.3	94.1	98.5	99.3	98.9	8.8	6.6	7.7	8.1	3.7	5.9	1.5	0.7	1.1
3– 4	99	75.8	79.8	77.8	89.9	92.9	91.4	98.0	99.0	98.5	24.2	20.2	22.2	10.1	7.1	8.6	2.0	1.0	1.5
5– 6	100	58.9	62.0	60.5	82.0	85.0	83.5	98.0	100.0	99.0	41.1	38.0	39.5	18.0	15.0	16.5	2.0	0.0	1.0
7– 8	89	38.2	46.1	42.1	83.2	86.6	84.9	95.5	96.6	96.0	61.8	53.9	57.9	16.8	13.4	15.1	4.5	3.4	3.4
9–10	59	42.3	49.2	45.7	88.2	89.8	89.0	100.0	100.0	100.0	57.7	50.8	54.3	11.8	10.2	11.0	0.0	0.0	0.0
11–12	26	50.1	54.1	52.1	76.9	73.1	75.0	96.1	100.0	98.1	49.9	45.9	47.9	23.1	26.9	25.0	3.9	0.0	1.9

TABLE 4.—Relation of Body Weight to Body Temperature and to Palpable Lymph Glands

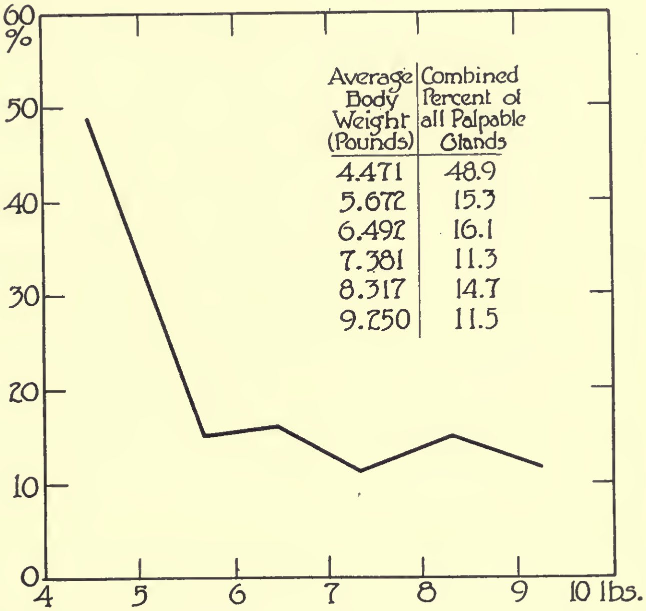
Body Weight, Pounds		No. of Cases	Average Body Temperature, F.	Palpable Lymph Glands											
				Inguinal				Occipital				Cervical			
				Right Absolute	Left Absolute	Average		Right Absolute	Left Absolute	Average		Right Absolute	Left Absolute	Average	
Range	Average					Absolute	Per Cent.			Absolute	Per Cent.			Absolute	Per Cent.
4– 5	4.471	15	98.0	13	11	12.0	80.0	8	8	8.0	53.3	2	2	2.0	13.3
5– 6	5.672	36	98.7	12	9	10.5	29.2	7	5	6.0	16.7	0	0	0.0	0.0
6– 7	6.492	151	98.4	58	51	54.5	36.0	18	14	16.0	10.4	5	1	3.0	2.0
7– 8	7.381	178	98.6	48	48	48.0	26.9	14	8	11.0	6.2	2	1	1.5	0.8
8– 9	8.317	59	98.5	21	17	19.0	32.2	8	5	6.5	11.0	1	0	0.5	0.8
9–10	9.250	13	98.0	3	2	2.5	19.2	2	2	2.0	15.3	0	0	0.0	0.0

TABLE 5.—Relation of Body Temperature to Palpable Lymph Glands

Body Temperature, F.		No. of Cases	Palpable Lymph Glands											
			Inguinal				Occipital				Cervical			
			Right Absolute	Left Absolute	Average		Right Absolute	Left Absolute	Average		Right Absolute	Left Absolute	Average	
Range	Average				Absolute	Per Cent.			Absolute	Per Cent.			Absolute	Per Cent.
97– 98	97.4	85	32	30	31.0	36.4	14	9	11.5	13.5	0	0	0	0.0
98– 99	98.7	256	102	81	91.5	35.7	33	25	29.0	11.3	9	5	7	2.7
99–100	99.2	78	18	18	18.0	23.1	5	4	4.5	5.8	2	0	1	1.3
100–101	100.3	14	3	3	3.0	21.4	0	0	0.0	0.0	0	0	0	0.0
101–102	101.1	3	0	0	0.0	0.0	1	1	1.0	33.3	0	0	0	0.0
102–103	102.1	3	1	1	1.0	33.3	1	1	1.0	33.3	0	0	0	0.0
103–104	103.3	5	1	1	1.0	20.0	1	0	0.5	10.0	0	0	0	0.0
104–105	104.0	1	1	0	0.5	50.0	1	1	1.0	100.0	1	1	1	100.0

new-born infants. If the percentage of the occipital, cervical and inguinal nodes is averaged (Chart 3), it is seen that 49 per cent. of all glands of the premature infant are palpable. Prematurity, therefore, increases the number of lymph glands which can be palpated in the new-born.

In order to determine whether body temperature is a factor in bringing about an increase in the percentage of palpable lymph glands, the percentage of discernible inguinal, occipital and cervical nodes was determined for each degree of temperature, Fahrenheit (Table 5). With the exception of one infant with a temperature of from 104 to 105 F., who showed a generalized lymphadenopathy, those infants with a normal temperature between 97 and 99 F. showed the highest percentage of lymph node involvement. A temperature of more than 100 F. in the new-born infant, therefore, does not necessarily mean infection with subsequent lymph node enlargement. On the contrary, some other factor than infection must play an important part in the enlargement of the lymph glands.



Average Body Weight (Pounds)	Combined Percent of all Palpable Glands
4.471	48.9
5.672	15.3
6.492	16.1
7.381	11.3
8.317	14.7
9.250	11.5

Chart 3.—Relation of palpability of inguinal, occipital and cervical lymph nodes to body weight.

Other factors which can account for the presence or absence of palpable nodes are considered in Table 6. Sex is the first to be eliminated. There is no difference between male and female. The percentage of inguinal glands enlarged in the male was 72 against 68 in the female, the average involvement being 70. Considering the comparatively few cases involved, no significance can be attached to a 2 per cent. variation above and below the average. The percentage of occipital and cervical glands does not show even minor differences between male and female.

Circumcision was performed on eighteen of the fifty-two boys. The foreskin was consequently somewhat swollen, and it was thought that the operation might account for a small percentage of the inguinal gland enlargement. Consequently, the circumcised boys were separated from the uncircumcised, and it was found that 70 per cent. of the circumcised and 74 per cent. of the uncircumcised (Table 6) showed discernible inguinal glands. This signifies that circumcision plays no part in the production of palpable glands and tends to prove that the lymphatic drainage of the genitalia has no material influence on the high percentage of inguinal nodes noticed in the new-born. To be sure, two girls had vaginal discharges, in one case proved to be gonorrheal in origin, and both had swollen inguinal nodes. The occipital glands of these babies, however, were enlarged also in both instances although they could play no possible part in lymph drainage of the genitalia. The cases were too few, therefore, to conclude that vaginal discharge is a significant factor in the etiology of palpable inguinal nodes.

Six babies had infected eyes. These cases were grouped and show apparently a relationship between the enlargement of occipital glands and eye infections. Eighty-three per cent. of the cases showed a distinct enlargement of the occipital and posterior auricular nodes, while only 21 per cent. without infected eyes had palpable occipital glands. The cases are too few, however, to correlate eye infections as an etiologic factor of occipital gland enlargements.

Temperature has already been discussed as a cause of nodal enlargement, and a glance at Table 6 shows that it plays a decidedly minor rôle. If one considers every temperature of more than 100 F. as abnormal and under 100 F. as normal, normal temperature of the new-born in the first week of life being approximately 99.5 F. according to Vierordt,[9] then rise of temperature shows only a slight correlation to increased lymph node involvement. In the case of inguinal glands, 76 per cent. are enlarged with high temperature and only 68 per cent. with normal. The occipital glands show no difference between high and low temperatures. The cervical glands show a decided variation, 12 per cent. being palpable with high temperatures and only 4 per cent. with normal. This correlation between high temperatures and enlarged cervical glands is probably brought about by mouth and pharyngeal infections which are accompanied by fever. Unfortunately,

TABLE 6.—CAUSATIVE FACTORS OF LYMPHADENOPATHY

Factors Associated with Lymphadenopathy	No. of Cases	Palpable Inguinal Nodes					Palpable Occipital Nodes					Palpable Cervical Nodes					Axillary Nodes, No.	Epitrochlear Nodes, No.	Mental Nodes, No.
		Right, No.	Left, No.	Both, No.	Average		Right, No.	Left, No.	Both, No.	Average		Right, No.	Left, No.	Both, No.	Average				
					No.	%				No.	%				No.	%			
Males	52	37	38	36	37.5	72	13	13	11	13.0	25.0	4	2	2	3.0	6	0	0	0
Females	50	35	33	32	34.0	68	14	10	10	12.0	24.0	4	2	2	3.0	6	0	0	0
Male and female	102	72	71	68	71.5	70	27	23	21	25.0	24.5	8	4	4	6.0	6	0	0	0
Circumcised	18	13	12	12	12.5	70	8	6	6	7.0	39.0	3	1	1	2.0	11	0	0	0
Uncircumcised	34	24	26	24	25.0	74	5	7	5	6.0	18.0	1	1	1	1.0	3	0	0	0
Cases with vaginal discharge	2	2	2	2	2.0	100	2	2	2	2.0	100.0	0	0	0	0.0	0	0	0	0
Infected eyes	6	5	4	4	4.5	75	6	4	4	5.0	83.0	1	0	0	0.5	8	0	0	0
Uninfected eyes	96	67	67	64	67.0	70	21	19	17	20.0	21.0	7	4	4	5.5	6	0	0	0
Temperature over 100 F. at some time	25	20	18	18	19.0	76	7	5	5	6.0	24.0	4	2	2	3.0	12	0	0	0
Temperature under 100 F. at all times	77	52	53	50	52.5	68	20	18	16	19.0	25.0	4	2	2	3.0	4	0	0	0
With jaundice	10	8	8	8	8.0	80	4	5	3	4.5	45.0	0	0	0	0.0	0	0	0	0
With moist cord stumps	4	2	2	2	2.0	50	1	1	1	1.0	25.0	0	0	0	0.0	0	0	0	0
Rectal bleeding	1	1	1	1	1.0	100	0	0	0	0.0	0.0	1	1	1	1.0	100	0	0	0
With any of the foregoing factors	52	41	39	39	40.0	77	16	14	12	15.0	29.0	6	3	3	4.5	9	0	0	0
With none of the foregoing factors	50	31	32	29	31.5	63	11	9	9	10.0	20.0	2	1	1	1.5	3	0	0	0

all cases of mouth and pharyngeal infections were not discovered, since only purulent discharges from the nose and mouth were recorded.

Icterus neonatorum is also a factor in lymphadenopathy. There were ten cases of jaundice in the 102 babies examined. Eighty per cent. of the jaundiced babies had palpable inguinal nodes, and 45 per cent. had discernible occipital glands. The number of cases is too small to conclude that icterus is a cause of lymph node enlargement.

Another possible factor which might cause enlargement of the inguinal lymph glands is a moist or an infected cord stump. Consequently, the cords were inspected at each palpation. Only four of the 102 babies showed a moist cord stump at some time, and of these four, 50 per cent. had enlarged inguinal glands. If bacterial invasion of the moist cord stumps had taken place, the inguinal lymph nodes which drain the umbilical region would undoubtedly be swollen. The dry cord stumps, however, apparently have a higher correlation with the swollen inguinal glands than do the moist umbilical stumps.

A close inspection of Table 6 shows an apparent difference between the number of glands on the right and left sides of the body. The nodes on the right side of the body apparently predominate over those of the left. The importance of this fact is questionable. The differences are too small and the number of cases are too few to establish the truth beyond question. No significance is attached, therefore, to the apparent difference between the right and left sides.

All the factors, with the exception of an infected throat, which might bring about lymphadenopathy have been considered. The surprising result is that these important factors influence slightly the production of lymph gland enlargement in the new-born. The average inguinal node involvement of male and female (Table 6) is 70 per cent., that of the occipital glands 24.5 per cent. and of the cervical glands 6 per cent. If all cases which are influenced by any accessory factor, such as sex, circumcision, infected eyes, fever and jaundice, are grouped as a unit, 77 per cent. of the inguinal nodes, 29 per cent. of the occipital nodes and 9 per cent. of the cervical nodes are palpable. If all the cases in which none of these factors exist are classed together, only 63 per cent. of the inguinal glands, 20 per cent. of the occipital glands and 3 per cent. of the cervical glands can be felt. This means that the factors mentioned above account for approximately one tenth of the inguinal gland enlargement, one fifth of the occipital nodes and one half of the cervical swellings. It is highly probable that if a close inspection for slight infections of the nasal and pharyngeal cavities had been undertaken all of the palpable cervical glands could be accounted for by known factors. The importance of this detail was not appreciated, however, at the time the data were accumulated.

CAUSES OF LYMPHADENOPATHY

The elimination of external factors which might cause lymph gland enlargement brings us to a consideration of other causes which might produce lymphadenopathy.

Enlarged cervical lymph nodes result from mouth, nasal and pharyngeal infections. This conclusion is supported by Jensen.[1] In a series of 240 new-born infants (Table 7) he found that 10 per cent. showed cervical gland enlargement the first day after birth, 6.6 per cent. on the second day, and the percentage of enlargement steadily diminished to 0.8 per cent. on the seventh day of postnatal life. He believed that mouth and nose infections, usually mild in character, were responsible for these cervical gland enlargements. Coerper[2] agrees with this point of view. He palpated 100 new-born infants (Table 7) and found 34 per cent. of the cervical glands. He believes that infection occurs most frequently in the nasal pharynx, associated with slight catarrh of the first part of the air passages and that the cervical nodes appear with the first sign of infection. The time of year and the amount of coryza may account for the high percentage of palpable cervical glands found in his series.

TABLE 7.—Results of Various Authors in Palpation of the Lymph Glands of the New-Born

Author	No. of Cases	Axillary Nodes		Occipital Nodes		Cervical Nodes		Inguinal Nodes		Cubital Nodes	
		Absolute	Per Cent.	Absolute	Per Cent.	Absolute	Per Cent.	Absolute	Per Cent.	Absolute	Per Cent.
Coerper.....	100	95	95	14	14.0	34	34	17.0	17	2	2
Jensen......	240	..	..	104	43.3	24	10	....	..	..	..
Baer........	25	majority		few	....	few	..	few	..	..	..
Gundoblin..	50	1	2	...	....	..	(Ca) 17	....	(Ca) 17	..	..
Dunn........	102	0	0	25	24.5	6	6	71.5	70	0	0

In respect to the axillary glands there is a wide variation of opinion. Of the 102 babies examined in our series not one axillary gland was palpable. Coerper, however, finds 95 per cent. of the axillary glands present. The five babies which had no discernible axillary nodes were all premature babies of 7 months. He states that the cause for the axillary gland swelling must lie in a process of the tributary field of this gland. But mastitis was found in only two cases and, consequently, the only cause he could assign for the remaining 93 per cent. was the physiologic breast gland swelling of the new-born. Baer[3] also noted the constancy of the axillary node swellings. He palpated the glands of twenty-five new-born infants ranging in age from 10 hours to 5 days and found that the axillary nodes were not only more constant but considerably smaller, while the occipital, cervical and inguinal glands occurred only in isolated cases. Hochsinger[10] and Gundobin[6] believed that Baer palpated small fat lobules in the axilla which he thought to be millet-sized axillary glands. It is our impression also that both Baer and Coerper were deceived as to the presence of lymph glands. The head of the humerus and large nerve trunks as well as fat lobules can readily be mistaken for the axillary nodes. In palpation of these glands in our series the investigator rotated the arm of the baby with one hand while with the fingers of the opposite he searched the axilla. By this means the head of the humerus could be felt gliding beneath the fingers, apparently increasing in size as a larger portion of the articular surface became subcutaneous. The nerve trunks could be differentiated from lymph nodes by palpating in two directions, across them and longitudinally.

Mental lymph nodes were not palpable in a single case in our series and none of the other investigators have made note of them.

Although epitrochlear glands were not found in a single instance in our experiment, several investigators have pointed out their occurrence. Grosser and Dessauer,[5] in a study of 1,066 infants, show that 66 per cent. of congenital syphilitic babies (fifteen in number), 19 per cent. of the rachitic infants (twenty in number) and 4.6 per cent. of the normal children had palpable epitrochlear glands. Hess [11] and Reiche [4] emphasized the value of the epitrochlears as an aid to the diagnosis of congenital syphilis. All three investigators grouped the new-born infants with infants of the first year. In the new-born infant, therefore, the significance of palpable epitrochlear lymph nodes is doubtful.

The occipital and inguinal nodes are still to be considered. The accountable factors which could influence the enlargement of the occipital lymph nodes are infected eyes and jaundice. We know by a consideration of Table 6 that of all the palpable occipital glands approximately 4.5 per cent. are caused by two factors, jaundice and eye infections. Patients with jaundice have 45 per cent. of palpable occipital nodes in contrast to a normal of 24.5 per cent. The six babies with eye infections show 83 per cent. of occipital enlargements. A certain percentage of occipital gland involvement might be accounted for by invasion of the tonsillar crypts by bacteria. Davis [14] and Goslar [15] have shown that bacterial flora invade the tonsils from twenty-four to seventy-two hours after birth and that plasma cells appear in the tonsillar crypts in about two weeks. The sudden increase of enlarged occipital glands from 11 per cent. on the tenth day to 25 per cent. on the thirteenth day is probably a result of tonsillar infection. The accessory factors, jaundice, vaginal discharge and high temperature, account for only 7 per cent. of swollen inguinal glands. The largest portion of occipital and inguinal lymph node involvement occurs as a result of some factor not considered heretofore. Some substance coming from the area drained by these glands must be responsible.

---

[14] Davis, D. J.: On Plasma Cells in the Tonsil, J. Infect. Dis. **10**:142 (March) 1912.

[15] Goslar, A.: Das Verhalten der lymphocytären Zellen in den Gaumenmandeln vor und nach der Geburt, Beitr. z. path. Anat. u. allg. Path. **56**:405, 1913.

What can this factor be? There seem to be four possible causes of inguinal lymph gland enlargement: (1) infection, (2) the sensitization of the new-born infant against the placental foreign tissue as suggested by Abderhalden, (3) a toxic material which might arise from the cord stump, and (4) absorption of a sterile foreign protein by the umbilical lymphatics.

1. Infection is the most common cause of lymphadenopathy. The cardinal signs of local infection are redness, heat, swelling and pain. None are present in the area about the dried stump of the cord. Infection, if severe, usually results in fever, but, as previously shown, the incidence of fever has no correlation with the enlargement of the inguinal nodes. Acute focal infection also gives rise to a leukocytosis in a large majority of cases. In order to see whether the enlargement of the inguinal lymph glands might be correlated with polymorphonuclear leukocytosis, blood counts were taken on fifteen infants about 5 days of age. This work was done by Lippman[16] in connection with a study of the blood of the new-born. Thirteen of the babies had palpable inguinal glands. The normal leukocyte count established by Lippman was 8,000 at birth, about 13,500 at 12 hours, and 3,000 by the fifth day of postnatal life. In all cases the blood count of those infants having palpable inguinal glands agreed with the normal. The curve of inguinal node involvement which rises steadily until the seventh day (Chart 2) is not correlated in any way with the change in the leukocyte count. All cardinal symptoms of infection are lacking in the normal infant, from 5 to 7 days of age, as well as a temperature and leukocytic reaction. Infection is ruled out, therefore, as a possible cause of inguinal lymph gland enlargement.

2. The sensitization of the new-born against the cord proteins is a possible cause of inguinal lymphadenopathy. Abderhalden[17] believed that foreign proteins stimulate the formation of protective substances which are capable of hydrolyzing this protein. These immunizing antibodies are specific and will react only against the inciting substances. If umbilical cord, therefore, is considered to be an antigen, just as Abderhalden believed placental tissue to be foreign protein, antibodies should be developed in the new-born infant against the cord proteins.

To prove the presence or absence of such antibodies, a fresh piece of umbilical cord was secured under sterile conditions. It was ground to very fine pulp and let stand for a week in physiologic sodium chlorid solution containing 0.25 per cent. of tricresol. The extraction was then titrated for one-tenth and one-fifth dilution against sheep's red blood cells and the one-fifth dilution found to be a satisfactory antigen. Samples of blood were taken from five babies (Table 8). They ranged from 3 to 13 days in age and all but one showed palpable inguinal glands. The blood samples were subjected to complement fixation tests which were carried out in a manner similar to that employed in a Wassermann test, except for the use of umbilical cord antigen. In all cases the tests were negative. The enlargement of the inguinal glands, therefore, could hardly be caused by the sensitization of the infant against attached umbilical cord.

---

[16] Lippman, H. S.: Unpublished thesis.

[17] Abderhalden, E.: Weiter Beitrag zur biologischen Feststellung der Schwangerschaft, Ztschr. f. physiol. Chem. **81**:90 (Oct.) 1912.

TABLE 8.—Complement Fixation Blood Reactions and Skin Anaphylactic Tests

Part A.—Fresh Umbilical Cord Used as an Antigen

			Weight, Gm.				Palpable Glands				
							Inguinal		Axillary, Occipital, Cervical		
Case No.	Sex*	Age, Days	At Birth	Present	Temperature	Cord Presence	Right	Left	Right	Left	Blood Reaction
103	♀	3	3,170	2,920	98.4	+	+	—	—	—	—
104	♂	6	4,310	4,260	98.4	+	—	—	—	—	—
105	♀	8	3,025	2,950	98.4	—	+	—	—	—	—
106	♂	8	3,330	3,000	98.2	—	+	—	—	—	—
107	♂	13	3,085	3,070	98.4	—	+	+	—	—	—

Part B.—Umbilical Cord Stumps Used as an Antigen

			Weight, Gm.				Palpable Glands							
							Inguinal		Occipital		Axillary Cervical Mental			
Case No.	Sex*	Age, Days	At Birth	Present	Temperature	Cord Presence	Right	Left	Right	Left	Right	Left	Blood Reaction	Anaphylactic Tests Inspected Daily for Four Days
108	♂	12	4,130	3,910	98.4	—	+	+	—	—	—	—	—	—
109	♀	8	4,055	4,200	98.6	—	+	+	—	—	—	—	—	—
110	♀	10	2,955	2,640	98.6	—	+	+	—	—	—	—	—	—
111	♂	10	3,450	3,480	98.4	—	±	±	—	—	—	—	—	—
112	♂	9	2,840	2,880	98.4	—	—	—	—	—	—	—	—	—
113	♂	10	3,860	3,840	98.4	—	+	+	—	—	—	—	—	—
114	♂	6	3,300	2,980	98.2	—	+	+	+	—	—	—	—	—
115	♀	12	2,063	2,040	98.6	—	+	+	—	—	—	—	—	—
116	♀	8	3,750	3,510	98.4	—	+	+	—	—	—	—	—	—

* In this Column ♀ represents female and ♂, male.

3. The cord stump, however, might contain degenerative products or toxic substances which would cause the inguinal nodes to become swollen. It is known that a toxin can bring about a lymph node enlargement. The effect of diphtheria toxin, for instance, has been studied by several authors. Barbacci[18] and Bulloch and Schmorl[19] come to

---

[18] Barbacci, O.: Ueber die feineren histologischen Alterationen der Milz, der Lymphdrüsen und der Leber bei der Diphtherie-Infection, Zentralbl. f. allg. Path. u. path. Anat. **7**:321 (May) 1896.

[19] Bulloch and Schmorl: Ueber Lymphdrüsenerkrankungen bei epidemischer Diphtherie, Beitr. z. path. Anat. u. allg. Path. **16**:247, 1894.

practically the same conclusion, namely, that lymph glands subjected to diphtheria toxin show a decided hyperemia and a high degree of hyperplasia of the gland parenchyma. Benzancon and Labbe[20] state that in an extreme case of glandular intoxication by diphtheria toxin the picture of necrosis predominates and that only in less severe cases or following the injection of diphtheria antitoxin does active reaction set in. Imamura,[21] studying the effects of tissue reactions of lymph glands to exotoxins, endotoxins and mixed toxins, came to the conclusion that the follicles react against free toxin, necrosis occurring; while against endotoxin, irritation and hyperplasia are the rule.

Since a toxic substance, especially a mildly toxic substance, stimulates a lymph gland to hyperplasia, it was necessary to investigate the cord stumps for such a material. Ten dried stumps were collected as they dropped off. They were macerated and extracted in a physiologic sodium chlorid solution containing 0.25 per cent. of tricresol. The extract was then titrated against sheep's red blood cells, the dilution of one-fifth being selected for the antigen. Blood was taken from nine babies (Table 8). The infants ranged from 6 to 12 days of age, eight of them having palpable inguinal glands. Anaphylactic tests were performed upon the babies using the Pirquet technic, the tuberculin being replaced by a drop of the extract. Complement fixation tests were made upon all the blood specimens, the newly prepared antigen being used. In all cases both blood tests and anaphylactic tests were negative. The enlargement of the inguinal lymph glands, therefore, could not be due to toxic substances in the cord stump.

4. The remaining cause of lymph adenopathy to be considered is the absorption of a sterile foreign protein. Practically no data are available concerning the effect of a sterile protein upon lymph glands. Gilbert and Carnot[22] state that occasionally with eruptions and serum therapy one sees a generalized lymphadenopathy explainable only as a reaction against a foreign protein. Further experimentation along these lines is beyond the scope of this paper. By elimination of infection and toxic causes, we feel justified in stating that, in all probability, the inguinal lymph nodes are enlarged because of the removal of the proteins in the cord stump by way of the lymph stream.

This theory, however, does not explain the enlargement at birth of 4.9 per cent. of inguinal glands and 3.95 per cent. of occipital glands.

---

20. Benzancon, F., and Labbe, M.: Effets comparés de l'action sur les ganglions du bacille et de la toxine diphtherie, Compt. rend Soc. d. biol. **50:** 507 (May) 1898.

21. Imamura, H.: Ueber die Gewebsreaktion der Milz und der Lymphdrüsen gegen Toxin, Verhandl. d. Jap. path. gesellsch. Tokyo, 1912, p. 65; abstr. Zentralbl. f. Bakteriol. u. Parasitenk. **60**:680 (March 17) 1914.

22. Gilbert, A., and Carnot, P.: Bibliothèque de thérapeutique, Paris, 1909, p. 201.

A survey of the thirteen cases (Table 9) in which swollen lymph nodes were palpated at birth shows that only one case of the thirteen was a premature infant, that the average temperature of the group was 98.4 F. and that, in only two instances, did the inguinal and the occipital glands become enlarged simultaneously. A certain percentage of the palpable glands in this group are undoubtedly due to the delay of one to three hours after birth before palpation of the lymph nodes. Lippman[16] has shown that a sudden and marked leukocytosis occurs in the first few hours after birth. Immediate palpation of the newborn infant would eliminate lymph node enlargement which might be due to this leukocytosis. The data of Jensen, which were determined immediately after birth, also show 7.5 per cent. of palpable occipital glands. He connects no pathologic significance to the findings of these glands and expresses his doubt that they have any connection with an hereditary constitutional anomaly. He points out that the glands were present in a case of cesarean section immediately after the extraction of the child and that this disproved the theory of traumatic or infectious origin in the birth canal. A small percentage of infants at birth show enlarged inguinal glands for which the etiology is as yet unknown.

TABLE 9.—Palpable Lymph Glands at Birth

Index No.	Right Occipital	Left Occipital	Right Inguinal	Left Inguinal	Weight Lb.	Weight Oz.	Temperature
9	+	0	0	0	6	5	98.0
41	+	+	+	0	7	1	98.6
64	+	0	0	0	8	5	99.0
75	+	0	0	0	8	5	98.0
79	+	0	0	0	6	6	98.0
86	+	+	+	+	7	9	98.8
21	0	0	+	0	6	15	98.2
29	0	0	+	0	6	6	98.0
39	0	0	+	0	8	10	99.0
67	0	0	+	+	4	5	97.6
76	0	0	0	+	6	15	99.6
77	0	0	0	+	7	2	....
78	0	0	+	+	6	7	97.6
Total	6	2	7	5	(Av.) 7	0	98.4

CONCLUSIONS

1. Daily curves of the percentage of lymph node enlargement show three distinct types: (*a*) the inguinal type which increases steadily from about 8 per cent. on the first day of life to 58 per cent. on the seventh day and then falls gradually to 48 per cent. on the eleventh day; (*b*) the occipital type which increases slightly from 6 per cent. on the first day to about 16 per cent. on the fifth day, descends slightly and then makes a sharp ascent to 25 per cent. from the ninth to the eleventh days, and (*c*) the cervical type which follows no definite course but oscillates between 0 and 4 per cent.

2. Occipital and inguinal lymph nodes are palpable at birth to the extent of 3.95 per cent. and 5.9 per cent., respectively. No cervical, axillary, mental or cubital glands, however, can be felt at birth.

3. Mental, cubital and axillary lymph glands were not palpable in any case throughout the entire series.

4. The high percentage of palpable axillary lymph glands found by Coerper and Baer was, in all probability, the result of identifying as a lymph node the head of the humerus or a nerve trunk.

5. The factors of sex and circumcision and the presence of moist cord stumps have no influence upon the incidence of lymph gland enlargements.

6. The factors of infected eyes and jaundice may have a slight correlation with the palpability of lymph glands.

7. Certain other factors associated with lymph node swellings of the new-born infant may be enumerated in the order of their importance thus: (*a*) infection of the nasal and pharyngeal passageways which causes most or all of the palpable cervical glands, (*b*) prematurity which is correlated with the presence of a higher percentage of palpable inguinal, occipital and cervical lymph nodes, and (*c*) high temperatures (above 100 F.) which are associated, to a slight extent, with the involvement of cervical and inguinal glands.

8. One tenth of the inguinal lymph nodes which are palpable in the new-born can be accounted for by the factors of infection, prematurity, temperature, jaundice, sex, circumcision or the presence of a moist cord stump.

9. One fifth of the occipital glands which are palpable in the new-born can be accounted for by the factors of infection, prematurity, high temperature, jaundice or infected eyes.

10. All of the cervical lymph nodes which are palpable in the first two weeks of life are caused, in all probability, by oral, nasal and pharyngeal infections.

11. The enlargement of inguinal lymph nodes is not due to infection.

12. The new-born infant develops no antibodies against the attached umbilical cord.

13. The new-born infant is not sensitized against the disintegrating proteins of the cord stump.

14. The new-born infant shows no toxic reaction against the foreign proteins of the cord stump.

15. A large percentage of inguinal lymph node enlargement is due, in all probability, to the absorption of sterile foreign protein from the dry cord stump.

BOOK REVIEWS

PELIDISI-TABLE. By Clemens Pirquet, M.D. Vienna and Leipzig: Josef Safàr, 1921 (English).

The table contains a short note describing how the nutrition index Pelidisi is obtained and how it can easily be found in the table when the sitting height and the weight of the child are known. The table is very useful. The sitting height is given in centimeters; the weight, in kilograms.

PRINCIPLES OF PROFESSOR PIRQUET'S SYSTEM OF NUTRITION. By Edmund Nobel. Pp. 15, with 1 illustration. Vienna and Leipzig: Josef Safàr, 1921 (English).

In this short treatise are given the principles of the Nem (Nutrition Element Milk) evaluation of diets, as well as the nutritive value of various foodstuffs, raw and cooked, and examples of how to plan suitable diets.

ANOMALE KINDER. By L. Scholz, M.D. Third edition, revised by Adalbert Gregor, M.D. Pp. 312. Berlin: S. Karger, 1922.

The book deals with the limits of mental health in children. "Anlage," heredity, degeneration, the causes of mental deficiencies, their somatic foundation and accompaniments are discussed. Various forms of feeblemindedness are described. Nervousness, hysteria and epilepsy are treated in separate chapters. Another chapter is devoted to chorea minor, for no very apparent reason. The sixty-four pages in which are considered the psychopathic children are perhaps the most interesting ones; but a discussion of the various groups into which these children are divided would exceed the limits of a review. The disturbances of the period of puberty and dementia praecox, with its two main divisions—hebephrenia and katatonia, are considered. The heading of one chaper is "Suicide." The pathologic basis of suicide is strongly emphasized. In the chapter on prophylaxis, the necessity of the prevention of marriage of unsuitable individuals is duly stressed and the necessity of complete abstinence from alcohol is emphasized unduly. Nearly one fourth of the book deals with various forms of treatment and welfare measures. A philosophic vein makes the book very attractive to many readers.

KURZES LEHRBUCH DER KINDERKRANKHEITEN. Heinrich Lehndorff, M.D. Second edition. Pp. 276. Vienna and Leipzig: Josef Safàr, 1922.

A rather liberal use of small print enlarges the scope of the book considerably beyond the limits of such abbreviated textbooks whose *raison d'être,* on the whole, is somewhat doubtful to the pediatrician. It is questionable whether such remarks as, "A dysfunction or hyperfunction of the thymus may be concerned with the sudden death in cases of status thymicolymphaticus," deserve even small print at this time. The abnormal thrombocytolysis in the reticulo-endothelial system as a factor in morbus maculosus werlhofii might be better established before its admission to the text. Some chapters, such as that on asthma and enuresis, need revision even for a short textbook. On the whole, the book is superior to the majority of similar short textbooks.

American Journal of Diseases of Children

Vol. 25 MAY, 1923 No. 5

A CRITIQUE OF THE PIRQUET FEEDING SYSTEM *

WITH SPECIAL REFERENCE TO ITS UNDERLYING PRINCIPLES

HAROLD K. FABER, M.D.
SAN FRANCISCO

About four years ago, I summarized [1] Pirquet's interesting methods of feeding that had been developed and introduced in Vienna during the Great War. A considerable literature dealing with this subject has since then been produced, and several enthusiastic writers have advocated the adoption of these methods in this country. The general feeling here has apparently been that the methods, while interesting, were so revolutionary that their introduction would involve an endless confusion, to be avoided if possible. Few critical studies of the methods themselves have appeared, and almost none in this country. The visit of Pirquet to this country in 1921 was followed by a reawakening of interest in the subject which has culminated in the appearance of his own description of the system in book form in English,[2] based on the Silliman lectures at Yale. It would appear timely, therefore, to give critical consideration to the outstanding Pirquet innovations, which are of importance, if for no other reason, because of the wide publicity they have obtained.

ACCURACY OF MEASUREMENTS OF SITTING HEIGHT

Since, with the exception of the nem, all the Pirquet methods are directly based on the sitting height, it is essential to determine the practical limitations of accuracy in determining this body dimension. Pirquet, in his "System der Ernährung" [3] states that, with some practice, the error of measurement is not in excess of 1 cm. This in itself is by no means negligible, since such an error will alter the pelidisi by nearly two points, and throw a child out of or into the group regarded

---

* Received for publication, March 26, 1923.

* From the Division of Pediatrics, Stanford University Medical School.

[1] Faber, H. K.: Von Pirquet's Feeding System, Am. J. Dis. Child. **19**:478 (June) 1920.

[2] Pirquet, Clemens: An Outline of the Pirquet System of Nutrition, Philadelphia, W. B. Saunders Company, 1922.

[3] Pirquet, Clemens: System der Ernährung, Berlin, Julius Springer, 1917.

as pathologically malnourished. It should be recalled that such a difference corresponds to from 5 to 10 per cent. of the body weight. Thus, a child only 5 per cent. underweight might, according to the direction of the error, be regarded as either 10 per cent. underweight or normal. Checked by the stem length in the series of sixty-five children, errors of 5 cm. in measuring sitting height were found, and Gray [4] has recently reported the same discrepancies. Essentially, these discrepancies are due, as Gray points out, to the fact that, in measuring sitting height, the child sits on the posterior muscles of the thighs, which may be contracted, increasing the sitting height; or relaxed, reducing it. An error of 5 cm. may alter the pelidisi index by 8 to 10 points, and the percentage index by 20 per cent. to nearly 50 per cent. In a 60 cm. child, it will alter the siqua by nearly 18 per cent., and the body surface, as calculated from the sitting height, nearly 19 per cent. The sitting height, therefore, is a dangerously inaccurate measure. It can be easily supplanted by the stem length of Dreyer, which appears to have many advantages of accuracy.

PELIDISI—THE PIRQUET INDEX OF NUTRITION

Estimates of the value of the pelidisi nutritional index based on clinical impressions vary so greatly that a final opinion cannot fairly be formed from a study of the literature; nor can a definite opinion as to its merits as compared with other indexes be formed on the basis of clinical data at present available. I have already shown [5] its serious lack of correspondence with the "percentage of normal weight" index commonly used in this country. Without attempting to add at present to the clinical impressions one obtains from the use of the Pirquet index, one may consider its basic structure, with a view to understanding its possibilities and limitations.

Pelidisi is the cube root of 10 times the body weight (in grams) divided by the sitting height in centimeters and multiplied by 100. Thus, an increase in weight (improved nutrition) is reflected by an increase in the nutrional index by the cube root of the gain, not by a direct proportion, as when percentage of normal weight is used. Growth in body length, on the other hand, is reflected in the index by direct proportion.

The normal or average pelidisi during most of childhood is about 94, as shown by Pirquet, Gray [6] and others, and not 100. Through the introduction of the factor 10 in the formula (equivalent to multiplication of the quotient by 2.15+), an intentional but nevertheless unfortunate resemblance to a percentage scale has been created which is very misleading. To understand the actual significance of pelidisi in terms of its apparent congener, the percentage of normal weight, a rather elaborate calculation is necessary. In Table 1, a comparison of the two scales has been made. The weight corresponding with a pelidisi of the normal 94 at a given sitting height was divided by weights corresponding with other values of the pelidisi for the same sitting height. This gives the percentages of normal weight corresponding with the various values of the pelidisi.

---

[4] Gray, H.: Sitting Height and Stem Length in Private School Boys, Am. J. Dis. Child. **23**:406 (May) 1922.

[5] Faber, H. K.: The Pirquet System of Nutrition and Its Applicability to American Conditions, J. A. M. A. **77**:1837 (Dec. 3) 1921.

[6] Gray, H., and Edmands, G. H.: Indices of the State of Nutrition in Children, Am. J. Dis. Child. **23**:226 (March) 1922.

TABLE 1.—*Relation Between Pelidisi and Percentage Under and Over Weight Ninety-Four Pelidisi Taken as Normal*

Pelidisi	Percentage of Normal Weight	Percentage Over or Under Weight	Difference Corresponding With One Point Pelidisi, per Cent.
80	61.6	—38.4	2.4
82	66.4	—33.6	2.5
84	71.4	—28.6	2.6
86	76.6	—23.4	2.7
88	82.0	—18.0	2.9
90	87.8	—12.2	3.0
92	93.8	— 6.2	3.1
94	100	0	3.3
96	106.5	+ 6.5	3.4
98	113.3	+13.3	3.5
100	120.4	+20.4	3.7
102	127.8	+27.8	3.8
104	135.4	+35.4	4.0
106	143.4	+43.4	4.1
108	151.7	+51.7	4.3
110	160.2	+60.2	4.5
112	169.2	+69.2	4.6
114	178.4	+78.4	4.8
116	187.9	+87.9	4.9

From a study of the table, it is at once apparent why, in certain studies, so small a percentage of children attained the apparently normal 100, since this value actually corresponds to 20.4 per cent. overweight, and why so large a percentage of children in one community which had reason to regard the average nutritional status of its children as good should have fallen into the Viennese category of "mild malnutrition,"[7] since, in any series of normal cases, approximately one half will fall below and one half rise above the average normal, in this case a pelidisi of 94, corresponding to 100 per cent.

Another important point to be noted in the table is that pelidisi cannot be readily—certainly, not mentally—translated into terms of percentage of normal weight. This is important because the latter is the common-sense interpretation of a nutritional index, its obvious and accepted meaning. It is clear, indeed, that Pirquet in devising his index used ten times the weight to simulate a percentage value with this idea in mind, and it has mislead many, if not most, of his followers.

Another important objection to the Pirquet index is the undue error introduced in it by relatively slight and common errors in measuring the sitting height, and the comparatively small effect made on it either by errors in weighing or by actual gains or losses in weight of considerable magnitude. Thus, an error of 1 cm. in measuring a 25 kg. child with a sitting height of 63 cm. will alter the pelidisi by 1.6 points, or about 6 per cent. in normal weight, a discrepancy greater than that caused by a difference of 1 kg. (2.2 pounds) in weight.

When the difficulties of measuring sitting height with even approximate accuracy are considered, it would seem unwise to accept for practical use a nutritional index with the inherent disadvantages named.

RELATION BETWEEN SITTING HEIGHT AND INTESTINAL AREA

Pirquet has laid great stress on the fundamental nature of his claimed direct relation between the square of the sitting height and the intestinal area. In his earlier publication, it is assumed to have the force of a natural law. The data on which he bases his claim are, however, very unconvincing, since they are derived from *averages* of sitting height and the mean of two rough estimates by Sappey of the area of the distended and undistended *small* intestine. Presenting no data at all as to individual variations of intestinal area, and no measurements of intestinal area and sitting height in the same individual, Pirquet's theory can scarcely be regarded as having any scientific validity; certainly nothing more than an indication of a possible general trend. Further, it is freely admitted by the author that because of villi, valvulae conniventes and other irregularities of the intestinal wall, it is practically impossible to determine the actual area of the intestinal epithelium. Indeed, in his last book he proclaims the relationship, formerly described as a natural law, as a "symbol," asking the reader to accept it as a matter of course. It is difficult for one who is only moderately critical to agree even to this extent. The evidence at hand justifies the conclusion that the existence of such a relationship is unproved and probably unprovable.

---

[7] Carter, W. E.: The Pirquet System of Nutrition and Its Applicability to American Conditions, J. A. M. A. **77**:1541 (Nov. 12) 1921.

RELATION BETWEEN INTESTINAL AREA AND FOOD REQUIREMENTS

That there is a direct relationship between intestinal area and food requirements is an important part of Pirquet's theory. The considerations of the preceding paragraph show that the former cannot be measured. Pirquet rests his argument on the pure assumption that the food requirements of the individual must correspond with the area from which food can be absorbed and not essentially with the amount of heat produced by the body from the food ingested. Such a theory of metabolism disregards certain well established facts:

1. All healthy organs possess a functional reserve, having more tissue or capacity of function than is called into use under ordinary conditions; and the amount of such reserve cannot be assumed *a priori*.

2. Different parts of the intestine have different rates of absorption and qualitative differences in the food materials absorbed.

3. The body may absorb more food than it actually requires, and either store or excrete the excess.

4. The heat output, together with the determination of retention and loss by excretion, has been convincingly shown by many metabolic experiments to be the true measure of the useful employment of food by the body, and hence of the food requirements.

The critical reader who is willing to be convinced must, without further proof, reject this part of Pirquet's theory.

RELATION BETWEEN SITTING HEIGHT, AND FOOD REQUIREMENTS AND BODY SURFACE

On the assumption that the sitting height squared is equal to the area of the intestine and that the latter stands in direct ratio to the individual's needs of food, Pirquet has provided a series of formulas for estimating food requirements from the sitting height which have apparently put to practical test the validity of his theories. There can be little doubt, since the Pirquet feeding method has been used on a tremendous scale over a considerable period of time, that it does give an approximate measure of the individual food requirements. Apart from the question as to whether this actually substantiates the Pirquet theories, it is a question of some importance whether the Pirquet method is a better one than those more commonly used, which are based on body weight, or body surface when accuracy is essential. As is well known, Rubner's theory that basal metabolism stands in relationship to body surface is based on experimental and clinical data, today widely accepted. Its validity has been recently reaffirmed in an emphatic manner by Lusk,[8] on the basis of careful test and check; and the findings of Benedict and Talbot,[9] though they establish a considerable normal variability, in general agree. Finally, the widespread clinical use of apparatus for measuring basal metabolism has given much further confirmation.[10] The average heat output during conditions of minimum normal (basal) metabolism, after infancy, is, roughly, 1,000 calories per square meter of body surface, or 0.1 calory per square centimeter. To this must be added certain quotas, conveniently expressed in percentages of the basal needs if desired, for growth, excretory waste, muscular activity, "cost of digestion" and so on.

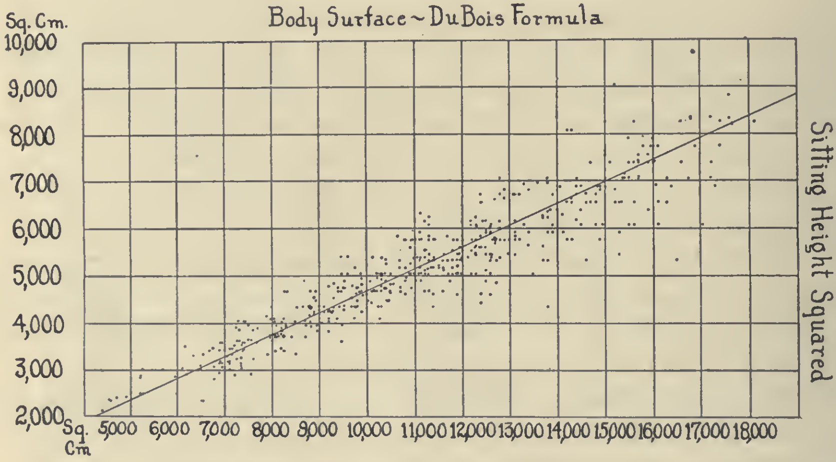


Chart 1.—Sitting height squared (Si^2) plotted against body surface (A) by the Du Bois formula, $A = W.^{425} \times H.^{725} \times 71.84$. The diagonal line represents $Si^2 \times 2.1 = A$ (500 cases).

Pirquet's formula for estimating basal food requirements, which corresponds with the needs for basal metabolism, is:

Three tenths nem × Si^2, when Si is the sitting height in centimeters. Since 1 nem equals two thirds of a calory, the formula can be expressed as:

$$0.2 \text{ calory} \times Si^2.$$

If we wish to compare the Rubner formula with the Pirquet, it is necessary to determine the relationship between the square of the sitting height and the body surface. The latter is now generally obtained with approximate accuracy from the Du Bois formula

---

[8] Lusk, Graham: Fundamental Ideas Regarding Basal Metabolism, J. A. M. A. **77:**250 (July 23) 1921.

[9] Benedict, F. G., and Talbot, F. B.: Metabolism and Growth from Birth to Puberty, Carnegie Inst. Washington Pub., No. 302, 1921.

[10] Progress of Clinical Calorimetry in the United States, editorial, J. A. M. A. **80:**184 (Jan. 20) 1923.

$$A = H^{.725} \times W^{.425} \times 71.84$$

conveniently applied by means of the special chart of Du Bois or that of Boothby.

Five hundred boys between the ages of 2 and 15 years were measured for height, weight and sitting height. Weight was taken in indoor clothing, with coats and shoes removed. The body surface was found by using the Boothby chart, and plotted against the sitting height squared, with the result shown in Chart 1.

It was found that the ratio of average sitting height squared to average body surface was about 1 : 2, or more exactly

$$A = 2.14 + \times Si^2$$

$$\text{or, } Si^2 = \frac{A}{2.14}$$

when A equals body surface in square centimeters.

This formula makes it possible to compare the Rubner and the Pirquet formulas. By interpolation

$$0.2 \text{ calories} \times Si^2 \text{ becomes}$$

$$0.2 \text{ calories} \times \frac{A}{2.14}, \text{ or } 0.093 \text{ calories} \times A.$$

Thus the basal requirements are 0.093 calories per square centimeter, or 930 per square meter.

It is therefore clear that the Pirquet formula for basal food requirements corresponds closely with Rubner's estimate, the former calling for about 930 calories per square meter and the latter for about 1,000.

Chart 1 shows clearly that there is a general trend toward correspondence between sitting height squared and body surface. For the lower values of both, the correlation is very close, but the "scatter" becomes much more marked for the larger values. Assuming, as I think we are justified in doing, that the Du Bois formula is reasonably accurate (probably the error is not more than 5 per cent.), the sitting height is a fairly accurate measure of the body surface in about 75 per cent. of cases, and it is an approximate measure of it in about 90 per cent. To this fact it seems reasonable to attribute such success as the Pirquet method has had in indicating food requirements.

It would be interesting to know whether a more accurate measure of trunk and head length would show a closer correspondence of values. The stem length, now generally preferred by anthropologists to the sitting height because it measures the distance between the bony points, and is not affected by contraction or relaxation of the posterior thigh mucles as is the sitting height, should be considered for this purpose.

A series of sixty-five children between the ages of 3 and 18 years were very carefully measured, undressed. The stem length, sitting height and weight were taken. Body surface was calculated directly from the Du Bois formula, not from the chart. The stem lengths squared were plotted against body surface, as shown in Chart 2.

Discrepancies between stem length and sitting height were found to range from 0 to 5 cm. The average prediction error of body surface calculated from the formula $A = St^2 \times 2.1$ (represented by the solid diagonal line in the figure) was ± 3.06 per cent., and the maximum error was 9.2 per cent. This degree of correlation is obviously much greater (though in a smaller series) than was found for sitting height squared in the first series, a fact readily explainable on the inherent inaccuracy of sitting height measurements.

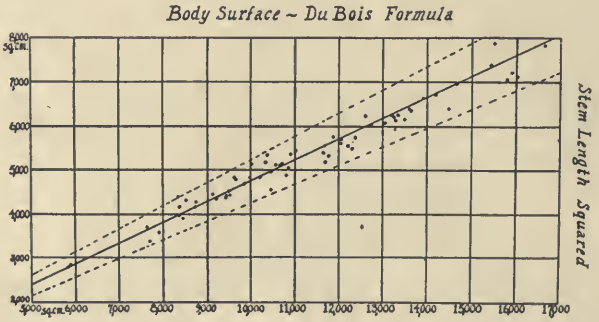


Chart 2.—Stem length squared (St^2) plotted against body surface (A). The solid diagonal represents $St^2 \times 2.1 = A$. The dotted lines denote a 5 per cent. variation (sixty-five cases).

It would appear, then, that body surface can be estimated during childhood with a certain degree of accuracy from the stem length, by a simple formula which can be applied without special chart, slide rule or logarithms, involving two simple multiplications only: $St \times St \times 2.1$

The usefulness of this formula is limited, since it must apply only to individuals of approximately normal conformation. Weight has a distinct influence on surface, and it is not considered in the foregoing formula. Morever, the factor 2.1 is not quite correct for the smallest or largest children; in the former, it is about 2.05; in the latter, about 2.2, and for adults it may well be about 2.3 or 2.4.

THE NEM

Pirquet's original reason for proposing a new unit of food value in place of the calory was a desire to increase popular understanding and use of the scientific measurement of food, in the hope that food, during the period of war scarcity, might be conserved. He believed that it would be impossible to popularize the calory not only because both the laity and medical profession were largely unfamiliar with the term and its meaning, but also because it was based on a conception of combustion which would never appeal to the popular imagination. If all foods could be compared with milk, on the other hand, the great advantage of visualization would be secured. Scientific accuracy would be secured by adopting as a standard a milk of certain composition having a value of 667 calories per liter. To a liter of such milk, the value of 1,000 nem (1 nem per cubic centimeter) was assigned. From the rather ingenious appeal of this conception, Pirquet has detracted, it seems to me, by his later argument that food should be considered in the light of units of intake, of assimilable energy, rather than as units of heat. The inference of his latest publication in English, that the calory implies the total combustible value of food rather than the energy available to the body from it, is, of course, quite untrue, unless considered as mere hair-splitting. Atwater and Kent[11] state that "by fuel value is meant the number of calories of heat equivalent to the energy which it is assumed the body would be able to obtain from a pound of a given material, provided the nutrients of the latter were completely digested." A direct comparison of Pirquet's nem values for food with Atwater and Kent's caloric values makes it clear that the former are merely converted from caloric values and not obtained by a new method. The essential meaning of the two terms is therefore identical, and the difference between them is merely arithmetical. One calory equals one and one-half nems. One nem equals two thirds of a calory.

It is true of the laity and medical profession in this country that the calory is generally understood and commonly used in practice. Physicians, nurses and dietitians constantly think of diet in terms of calories, and the same may be said of the thousands of lay people who are ridding themselves of superfluous flesh by "counting their calories."

So distasteful is the prospect of substituting a new unit of any kind for one already established that the change could be brought about only by overwhelming advantages to be gained. That such advantages are to be had from adoption of the Pirquet food unit, at least in this country, I see no reason to believe. That the nem will ever be generally adopted here is highly improbable, but efforts to have it adopted, while doomed to failure, are certain to lead to confusion, both within and without the profession. Finally, if one wishes, he can visualize fuel values of foods as ounces of milk by dividing the calories by 20.

---

[11] Atwater and Kent: The Chemical Composition of American Food Materials, p. 14.

CORRELATIONS OF HEIGHT, SITTING HEIGHT AND WEIGHT

As an appendix to the discussion of methods based on sitting height, Table 2 presents coefficients of correlation and correlation ratios.[12] The data from which they have been computed consist of measurements of the 500 boys already mentioned.

The figures show clearly that height is more closely correlated with weight and with the cube root of weight than is sitting height. The one advantage shown by sitting height (confirming Pirquet) is that its general relation to the cube root of weight is linear, while that of height is curvilinear. In other words, sitting height shows rather roughly a simple arithmetical relation to the cube root of weight, independently of size (and hence, of age), which is not true of standing height. Quite outbalancing this advantage is the superior reliability of the relation of height both to weight and to the cube root of weight. The very practical inference is to be made that height-weight standards of nutrition are more reliable than sitting height standards. The same may not be true of stem length, but certainly we are not yet in a position to adopt this measure as a standard. For the present at least, every consideration favors the continuance with such modifications as shall be shown necessary of the height-weight standards now in general use in this country.

TABLE 2.—*Coefficient of Correlation and Correlation Ratios*

	Coefficient of Correlation (r)	Correlation Ratio (η)	Blakeman's Criterion
Height-Weight.............	0.898 ± 0.006	0.964	5.88
Sitting Height-Weight......	0.857 ± 0.008	0.900	6.77
Height-$\sqrt[3]{}$ Weight...........	0.903 ± 0.006	0.994	6.91
Sitting Height-$\sqrt[3]{}$ Weight....	0.882 ± 0.007	0.876	0
Sitting Height-Height......	0.921 ± 0.005	0.934	2.97

SUMMARY AND CONCLUSIONS

Practical and theoretical reasons both militate against the general adoption of the Pirquet system of feeding. The sitting height on which it is based cannot be measured with sufficient accuracy, and even slight errors in this measurement lead to serious errors in calculating the nutritional status of the individual and his food requirements. The Pirquet index of nutrition has a misleading resemblance to a percentage of normal weight, into which it cannot readily be translated. The Pirquet theory that sitting height and intestinal area are in close correspondence is neither susceptible of proof nor consonant with probability. Its corollary, that sitting height and food requirements bear a relationship to each other, while based on false premises, is probably true, but depends for its validity on the fact that sitting height and body surface show a certain degree of correlation. This correlation is not close enough to permit the accurate calculation of body surface from sitting height. Finally, the introduction of Pirquet's food unit, the nem, to supplant the calory is highly undesirable, largely for practical reasons, and presents no advantages that would appeal to the American public.

---

[12] The coefficient of correlation (r) and the correlation ratio (η) both show, on a scale of 0 to 1.0, the degree of relationship between two variables, such as height and weight. If, when these variables are plotted against each other on ordinate paper, the general trend is about a straight line, both the coefficient of correlation and the correlation ratio express the relationship. If the general trend is about a curved line, the correlation ratio (η) alone expresses it. Hence, if ratio and coefficient are quite similar, the trend is along a straight line. If separated, the trend is along a curved line. Blakeman's criterion, expressing the difference between ratio and coeffiicient, must be 2.5 or less, if the distribution is to be regarded as linear.

MONGOLISM IN ONE OF TWINS AND THE ETIOLOGY OF MONGOLISM *

T. HALBERTSMA, M.D.
HAARLEM, HOLLAND

That the occurrence of mongolism in twins must be regarded as important and that it may possibly throw light on the etiology are admitted by all authors that have studied this affection. Since the publication of Fraser's [1] paper, ten cases of mongolism in one of twins and two cases in both have been reported. I have been able to add to this series five new cases in which only one of the twins was a mongolian idiot.

A study of the literature reveals that almost nothing is known about the causation of mongolism. Several authors have regarded the affection as dependent upon diseases of the mother, or as acquired during pregnancy through the operation of other influences injurious to the embryo. The only fact that can be asserted as having etiologic significance is that the great majority of mongolians are the children of mothers who are nearing the end of the child-bearing period. For this reason these children are often the last of large families. Other congenital abnormalities are often encountered.

Shuttleworth [2] has spoken of mongolians as "exhaustion products"; but it seems to me that this term is only another expression of the etiologic factor of old mothers. Thomson [3] says that it seems that something goes wrong in very early uterine life—probably by the second month, judging from the nature of the cardiac defects.

Van der Scheer [4] has spoken of mongolism as belonging to that type of malformation in which there is a central defect of the head, such as cyclopia, cebocephalia and arhinencephalia. McLean [5] described recently a mongoloid appearance in one of twins. He said that if the condition of the mother during pregnancy were related to the etiology one should always expect that the identical pathologic condition would be present in both twins.

I have come to the same conclusion, and I will endeavor to show in this paper that mongolian idiocy is of germinal origin, and that the

---

* Received for publication, Jan. 31, 1923.

1. Fraser and Mitchell: J. Ment. Sc., 1877.
2. Shuttleworth, G. E.: Brit. M. J. **2**:661, 1909.
3. Thomson in Garrod, A. E.; Batten, F. E., and Thursfield, Hugh: Diseases of Children, New York, Longmans Green & Co., 1913.
4. Van der Scheer: Psychiat. en Neurol. Bl., 1918.
5. McLean, Stafford: Mongolian Idiocy in One of Twins, J. A. M. A. **78**: 13 (Jan. 7) 1922.

theories that accept the possibility of an acquired origin during intrauterine life are untenable.[6]

REPORT OF CASES

CASE 1.—Baby L., aged 10 months, was one of twin boys born when the mother was 38. Their birth marked the sixth pregnancy. The patient was a typical mongol; the other child was normal in every respect. Measurements of the head of the mongol were: greatest length, 12.5 cm., greatest breadth, 12.5 cm., horizontal circumference, 40.5 cm. The mongol's weight was 3,700 kg. He could not sit unsupported, did not speak and had no teeth as yet. The Wassermann reaction was negative. At the birth of the twins two placentas were seen, and each child had its own chorion and amnion.

CASE 2.—Baby v. L., aged 4½ months, was one of twin girls. The mother was 41 at the time of their birth. This marked the fourteenth pregnancy; there had been three miscarriages. There were two well separated placentas, with two chorions and amnions. The Wassermann reaction was negative. The measurements of the head of each twin immediately after birth (measurement of mongolian mentioned first) were: greatest length, 46 and 48 cm.; greatest breadth, 9 and 9.5 cm.; horizontal circumference, 30 and 33 cm.; weight, 2,600 and 2,800 kg. The mongolian was typical. She showed as an accompanying deformity a preauricular appendage on the right, and was in such bad condition that she soon died of bronchopneumonia. The twin sister is normal.

CASE 3.—Baby R., aged 2½ years, boy, a mongolian idiot was one of twins, the sister being normal. The mother was 43 when the children were born. Their birth marked the seventh pregnancy. The mongol was clubfooted on both sides; the girl was absolutely normal.

CASE 4.—Baby v. B., aged 2½ years, boy, a mongolian idiot, was one of twins, the girl being normal. The mother was 38 at the time of their birth; the father was 48 years of age. The mongolian was typical; the girl showed no abnormalities.

CASE 5.—Baby J. L., aged 4 years, boy, twin, presented a typical mongolian appearance. The mother was 44 years of age when the mongol was born (ninth pregnancy). At the end of the third month of pregnancy there was a miscarriage; six months afterward, the mongol was born at term. The idiot child sat unsupported at 1½ years, dentation began at 3 years. The child now has a pigeon-breast.

COMMENT

It is evident that all of these cases of mongolian idiocy resulted from a so-called two-egg pregnancy. As is known, twins are of two types. The one-egg, or identical, twins are derived from a single egg, which has formed two embryos. They are always of the same sex, are enveloped in the same chorion, and there is only one placenta. The children show marked resemblance. As the entire heritable nature is common to both, germinal affections will be equally present in both. I refer to twins with epilepsy and asthma. Acquired diseases of which the cause may be sought in the condition, such as syphilis, of the mother during pregnancy will also manifest themselves in both. In the two-egg, or fraternal, twins, there have been two eggs which were fertilized separately. Each embryo is enveloped in its own chorion, and they are no more closely related than ordinary brothers and sisters; their sex may be different or the same. One of them may be affected by an inheritable disease (achondroplasia), while the other is absolutely normal. Diseases of the mother that might affect the embryo (syphilis) will generally manifest themselves in both twins, although the symptoms may vary.

---

[6] Cases 1 and 2 were observed at the Leiden Pediatric Clinic by the author. For the data concerning Cases, 3, 4 and 5, the author is indebted to Dr. W. M. van der Scheer, Inspector of Lunatic Asylums in Holland.

We may now return to our problem, and ask whether mongolism is germinal in origin or acquired. If mongolism were not germinal in origin but acquired, then the occurrence of mongolism in one of twins would be a surprise. A review of the literature revealed fifteen such cases, and only two cases of mongolism in both twins. It would be difficult to imagine how one child could remain absolutely normal, while the other showed the numerous and universal symptoms of mongolism.

TABLE 1.—Cases of Mongolism in One of Twins

No.	Author	Sex of Twins	Type of Twin-Birth
1	Fraser (J. Ment. Sc., 1877)	"The mongol was one of twins"	Unknown
2	Hultgren (Nord. med. Ark., 1915)	Mongol boy; normal girl	Two-egg
3	Neumann (Berl. klin. Wchnschr., 1899)	Mongol boy; normal girl	Two-egg
4	Cassel (Berl. klin. Wchnschr. **54**: 159, 1917)	Mongol boy; normal girl	Two-egg
5	Cassel (ibid.)	Mongol girl; normal boy	Two-egg
6	Shuttleworth (Brit. M. J. **2**:661, 1909)	Mongol girl; normal boy	Two-egg
7	Comby (Arch. de méd. d. en. **20**: 505 [Oct.] 1917; cont. **20**:561 [Nov.] 1917; cont. **20**:617 [Dec.] 1917)	Mongol girl; normal boy	Two-egg
8	Weigall (quoted by Comby)	? ?	Unknown
9	Swanberg-Haynes (Arch. Neurol. & Psychiat. **1**:717 [June] 1919)	Mongol boy; normal girl	Two-egg
10	McLean (J. A. M. A. **78**:13 [Jan. 7] 1922)	Mongol boy; normal girl	Two-egg
11	Halbertsma	Mongol boy; normal boy	Two-egg
12	Halbertsma	Mongol girl; normal girl	Two-egg
13	Halbertsma	Mongol boy; normal girl	Two-egg
14	Halbertsma	Mongol boy; normal girl	Two-egg
15	Halbertsma	Mongol boy ?	Two-egg

If, however, mongolism is due to defects inherent in the germ plasm, then the occurrence of mongolism in one of the twins is comprehensible; but it will only be possible in a two-egg pregnancy. The hypothesis would be untenable if one could show twins resulting from a one-egg pregnancy of whom one was a mongol and the other was normal. It will be difficult in a case of mongolism in twins to determine whether the condition resulted from a one-egg or two-egg pregnancy unless the sex is different, or unless one can secure information about the fetal membranes and the placenta—as was possible in my cases.

An examination of the cases from the literature revealed that, in accordance with the theory, in all cases of mongolism in one of twins, the two-egg pregnancy was evident, for in all cases the sex was different (no data about two cases).

TABLE 2.—Cases of Mongolism in Both Twins

No.	Author	Sex of Twins	Type of Twin-birth
1	Hjorth (quoted by Shuttleworth, Footnote 2)	Same sex	One-egg (?)
2	de Bruin (Nederlandsch. Tijdschr. v. Geneesk, 1902)	Two mongol boys	One-egg (?)

If we now consider the cases of mongolism in both twins, the germinal theory makes the birth of these twins possible only in case of one-egg pregnancy. Although a two-egg pregnancy in these cases is imaginable, as the result of the coincidence of two separate eggs both doomed to mongolism, this will occur very seldom, as mongolism in more than one child of the same mother is almost never reported. In this connection, it was interesting that in the only two cases reported the twins were of the same sex. Cases of twin mongols of different sex do not exist.

SUMMARY

The conclusion that mongolism is germinal in origin is deduced from the fact that mongolism occurs in one of twins. An examination of these cases reveals that all have resulted from a two-egg pregnancy. Cases of mongolism in both twins of different sex are unknown; of like sex, there are cases described, which is in accordance with the theory that mongolism has to be regarded as the result of defects inherent in the germ plasm.

ULCERATIVE STOMATITIS AND ITS TREATMENT BY THE INTRAVENOUS INJECTION OF ARSENIC*

EDWARD A. MORGAN, M.B.
TORONTO

Those who were in the service during the recent war and particularly those who served in any one of the fields of battle will recall the disease which was more or less prevalent among the rank and file and which was popularly known as trench mouth. The condition was not serious in that it did not impair the man's fighting efficiency, but it was annoying because of its contagiousness and its resistance to treatment. The frequency with which this condition has been encountered during the last two years among the children of this city has excited no little comment. It is designated by several names: suppurative gingivitis, Vincent's angina, trench mouth and ulcerative stomatitis. The latter term has been used, however, to describe two conditions which, I believe, are not identical either etiologically or clinically, but which frequently coexist in the same patient.

The terms Vincent's angina, trench mouth and suppurative gingivitis refer to an acute infection of the gums by spirilla and fusiform bacilli, producing certain local signs, such as spongy, bleeding gums, necrotic areas in the immediate vicinity of the teeth and general symptoms, such as malaise, pyrexia and anorexia. The term ulcerative stomatitis, although used to describe a similar condition, is also used to describe the disease characterized by the formation of small ulcers on the tongue or buccal mucous membrane without involvement of the gums. These ulcers are usually superficial and covered by a grayish exudate but lack the ragged necrotic appearance which characterizes the ulceration of the gums referred to above. Although this variety of stomatitis is frequently seen in combination with Vincent's infection of the gums it is, in all probability, not one and the same infective process.

ETIOLOGIC FACTORS

The predisposing causes of suppurative gingivitis are lowered vitality and oral uncleanliness. Such a lowering of vitality is liable to occur after any one of the infectious diseases or even following an acute upper respiratory infection. Several writers have emphasized its increased frequency during the cold months, though the reason for this

---

* Received for publication March 16, 1923.

* From the wards and outpatient department of the Hospital for Sick Children.

is not very obvious. The exciting cause is an infection of the gums by Vincent's organisms. Smears from the purulent material which exudes from the margin of the gums show large numbers of spirilla and fusiform bacilli, some necrotic material and a striking paucity of polymorphonuclear leukocytes.

Convincing experimental proof has been advanced to show that the spirillum and fusiform bacillus are actually pleomorphic forms of the same organism.

The importance of oral uncleanliness as a predisposing cause has been satisfactorily demonstrated by a comparative bacteriologic study of the mouths of persons with normal and with decayed teeth. Smears from the buccal mucous membrane of fifty normal mouths gave only one positive result for Vincent's organisms. Smears from the teeth of twenty-five normal persons gave four positive results, whereas smears from diseased teeth of a large number of persons gave 90 per cent. positive results.[1] It requires, therefore, no stretch of the imagination to picture these organisms lurking in carious teeth waiting for the lowering of the body resistance which will enable them to invade and infect the gums.

EPIDEMIOLOGY

Although the infection is, in many cases, autogenic, it is very readily transmitted from one person to another. It is not uncommon to find several cases in one household or in one school or even along one street. In the series of cases reported in this article, five occurred in separate houses in one locality, and the infection was traced to a boy 12 years of age. The two principal modes of transmission are kissing and the use of food utensils which have been carelessly washed. All persons with dental caries must be considered carriers of the disease in view of the bacteriologic findings enumerated above. On several occasions during the last year, the only source of infection which could be discovered was the presence of carious teeth in either parent, and in one case in private practice smears taken from the mother's teeth revealed large numbers of spirilla and fusiform bacilli.

SYMPTOMATOLOGY

The onset of the condition is usually sudden. Undernourished children are more frequently attacked, or children that are debilitated as the result of some acute infective fever. There is a general malaise and a slight elevation of temperature seldom above 101 F.

Anorexia is an early and constant symptom, the child refusing all solid food; even liquids are taken sparingly. The breath is very offensive, the odor being identical with that given off from any putrefactive process. The gums are deep red or purplish and heaped up around the teeth; they bleed very readily at the slightest touch, and, if the disease has been of four or five days' standing, there are often areas of necrosis along the gum margin. At times similar areas of necrosis are seen under the tongue, on the buccal mucous membrane or even in the faucial region. Pressure on the gums may cause blood-stained pus to exude along the free margin. The diseased parts are painful and tender to the touch, and the child resents vigorously any attempt at examination. If untreated or improperly treated, the process extends into the alveolar sockets, resulting in the loosening and falling out of the teeth. As a rule, the lymphatic glands below the jaw are enlarged and tender, but actual necrosis of the glands is rare.

---

[1] Reckord, F. F. D., and Baker, M. C.: Vincent's Angina Infection: Its Prevalence, Manifestations, Bacteriology and Treatment, J. A. M. A. **75**:1620 (Dec. 11) 1920.

TREATMENT

Prior to the recognition of this disease as a spirillum infection, the treatment consisted of the local and internal administration of potassium chlorate. During recent years, however, the employment of some form of arsenic in solution has been advocated, the most popular formula being known as Bowman's solution, which consists of solution of potassium arsenite, 12 c.c.; wine of ipecac, 12 c.c., and glycerin, 8 c.c. This was painted on the inflamed gums several times daily, but although the relief was immediate it was not always permanent. In other words, local arsenical applications did not appear to reach the deeper foci of infection, and the process tended to recur as soon as treatment lapsed. It seemed reasonable to assume that arsenic administered intravenously would be more apt to reach these deep foci and thus effect a more lasting cure.

Twenty-five cases have been treated in this manner in the last eleven months, and the results of treatment have been always satisfactory, and at times spectacular. All of the children were more than 1 year of age and 87.5 per cent. were more than 2 years. There were no instances of the disease occurring in children before the eruption of teeth.

In eight cases Bowman's solution was used locally in conjunction with an intravenous injection of an arsenical salt such as neoarsphenamin. Improvement was marked in from two to four days, and cure was effected in an average of five and three-fourths days.

In seventeen cases no treatment was used other than the intravenous injection. One of these children was suffering, at the time of injection, from an acute intestinal intoxication, and died a few hours afterward. Among the others improvement was noted on an average two and one-half days after injection, and complete cure was recorded on an average of five and three-eighths days. In two cases, eleven and thirteen days, respectively, elapsed before recovery was complete, and both these children required two intravenous treatments. One child that had been treated for eighteen days with local applications of Bowman's solution without visible improvement was completely cured eight days after intravenous medication was given. A short summary of one of the most severe cases is worth recording.

REPORT OF CASE

A boy, aged 12, was admitted to the surgical ward of the Hospital for Sick Children with a history of swelling of the lower jaw of three days' duration and of a sore mouth for five days. Examination revealed a probable osteomyelitis of the inferior mandible. An operation was performed and a quantity of foul smelling pus was evacuated through an incision in the left submaxillary region. It was difficult to obtain a satisfactory view of the teeth and gums since the child could not open his mouth without considerable pain; but the gums about the upper and lower incisors and bicuspids were purple, and there was extensive necrosis along the free margin.

The lymphatic glands below the jaw, particularly on the left side, were swollen sufficiently to produce marked disfigurement. Two days after the injection of 0.3 grain of sodium arsphenamin the child could open his mouth without discomfort and eat semisolid food, and in four days recovery was practically complete, though there was still some discharge through the operation wound.

COMMENT

In ten of the twenty-five cases there were, in addition to the gingivitis, small ulcers on the tongue or on the internal aspect of the cheeks similar to those described at the beginning of this article. In six of the ten cases these ulcers were benefited little if at all by the arsenical medication, since they persisted for several days after the gums had completely healed. In these instances, the administration of potassium chlorate was followed by healing of the ulcers in from two to five days. It seemed probable that this process was not due to an infection by Vincent's organisms, and this impression was considerably strengthened when four additional cases presenting only ulcers answering the foregoing description were examined bacteriologically. In none of the four cases could spirilla or fusiform bacilli be demonstrated, and none of them showed any improvement following an intravenous injection of arsenic. The smears from these ulcers showed, as a rule, numerous pus cells which seemed to point to the probability of an infection by one of the pyogenic organisms.

CONCLUSIONS

1. Twenty-five cases of ulcerative stomatitis due to infection by Vincent's organisms were treated by arsenical compounds either intravenously alone, or combined with local applications. One patient died shortly after the injection as the result of an intercurrent disease. The other twenty-four were cured in an average of five and one-half days after the first injection. The cure in every case appeared to be permanent.

2. In 40 per cent. of the cases the gingivitis was accompanied by ulceration of the mucous membrane of the tongue and inner aspect of the cheeks. These ulcers, as a rule, did not appear to respond readily to the arsenical medication, and it is probable that they were not a manifestation of the same infection which produced the gingivitis but rather the result of a secondary pyogenic infection.

THE TREATMENT OF VASCULAR NEVI WITH RADIUM *

R. H. RULISON, M.D., AND STAFFORD McLEAN, M.D.
NEW YORK

Vascular nevi may be divided, from the standpoint of radium therapy, into four types: (1) flat angiomas, superficial and level with the skin; (2) flat angiomas, level with the skin but deeply infiltrating the cutaneous and subcutaneous tissue or mucous membrane; (3) angiomas which are elevated to a greater or less degree with smooth and papillated surface; (4) soft and pulsatile angiomas with fluctuating areas, and (5) erectile angiomatous tumors situated under the skin or in the mucous membrane.

Most of the cases that came under our observation belong in the third group, some in the fourth and fifth groups and a few in the second group. The few attempts made to treat the superficial flat angiomas (port wine marks) with radium met with indifferent success and were not continued for sufficient time to warrant comment.

The type of lesion treated in this study may be classed as raised capillary hemangiomas. Some, however, were markedly pulsatile; nearly all showed distention on exertion and might correctly be considered clinically as cavernous hemangiomas.

These lesions are really congenital; but the term is somewhat confusing, as angiomas are frequently insignificant at birth and occasionally are not noted until the second or third week of life. A certain number disappear spontaneously; but a larger number tend to increase rapidly in size as age advances. The color is usually a violaceous red, but may vary from a bright red to a deep violet. The surface may be smooth but is usually rugose. The skin over the lesion is thin and easily traumatized, so that ulceration and hemorrhage are frequently noted.

The majority of the patients were infants or young children from the outpatient service of one of us at the Babies' Hospital. Others were referred from the service of Dr. J. A. Fordyce at the Vanderbilt Clinic. The treatment was given in the dermatologic service of the outpatient department of the Presbyterian Hospital, New York. These cases were naturally selected as being best suited for radium treatment. The lesions amenable to other forms of therapy were referred to surgeons or treated by other dermatologic methods. The radium used was in the form of tubes of 25 and 50 mg. No filtration was used other than the silver capsule in which the glass tube of radium is contained.

---

* Received for publication, March 26, 1923.

An effort was made to regulate the dosage and the quality of rays by varying the distance between the tube and the skin. The tubes were embedded in a square of wax and attached to the skin by straps of adhesive tape. Dental wax is sold in sheets one-sixteenth inch thick and, when warmed in hot water, is easily molded into any desired form. The wax usually interposed between the radium and the skin was from one-eight to one-half inch thick. The duration of a single application varied between one-half and two hours, and the amount of radium used varied between 25 and 200 mg. When more than one tube was utilized, care was taken to see that the tubes were separated by a distance of at least 1 cm. An effort was made to secure a cross-fire effect by applying the radium tubes on opposite sides of the nevus when the lesion was in a favorable location or sufficiently raised to allow it. No treatments were given without an interval of at least three weeks, and, if any skin reaction was noted at the end of this period, the treatment was deferred until all inflammatory signs had disappeared.

*Location of Lesions Treated in Thirty-Three Cases**

Head:			26
Scalp		4	
Ear and adjacent integument		4	
Face			
Forehead	5		
Eyelid (upper)	3		
Eyelid (lower)	2		
Cheek	5		
Lip (upper)	1		
Lip (lower)	2		
		—18	
Body:			17
Shoulder	1		
Chest (anterior)	3		
Abdomen	2		
Back	2		
Arm	3		
Hand and Fingers	1		
Buttocks	2		
Thigh and Leg	3		
		—17	
Total number of lesions treated			43

* Three of these patients had multiple nevi; one patient presented five.

No claim is made that the method of using radium in these cases was ideal. Some authorities believe that all these lesions should be treated with radium plaques and that certain types should be treated with toiles. Many radium workers always use filtration with brass, lead, wood, paper, etc. An effort was made to secure satisfactory results without filtration (except such as could be secured by distance) because the whole subject of filtration is in such an indefinite state that it is hard to estimate the dosage actually delivered through various substances of variable thickness at varying distances. The use of filters of any potency calls for such a lengthening of the time of individual treatments that it would be impracticable at a clinic where a number of cases had to be treated in the course of a few hours. In private practice larger doses with a longer interval between treatments and with distance somewhat increased seem desirable; but no damage other than superficial exulcerations in one or two cases has been noted. These healed without inconvenience or noticeable scarring.

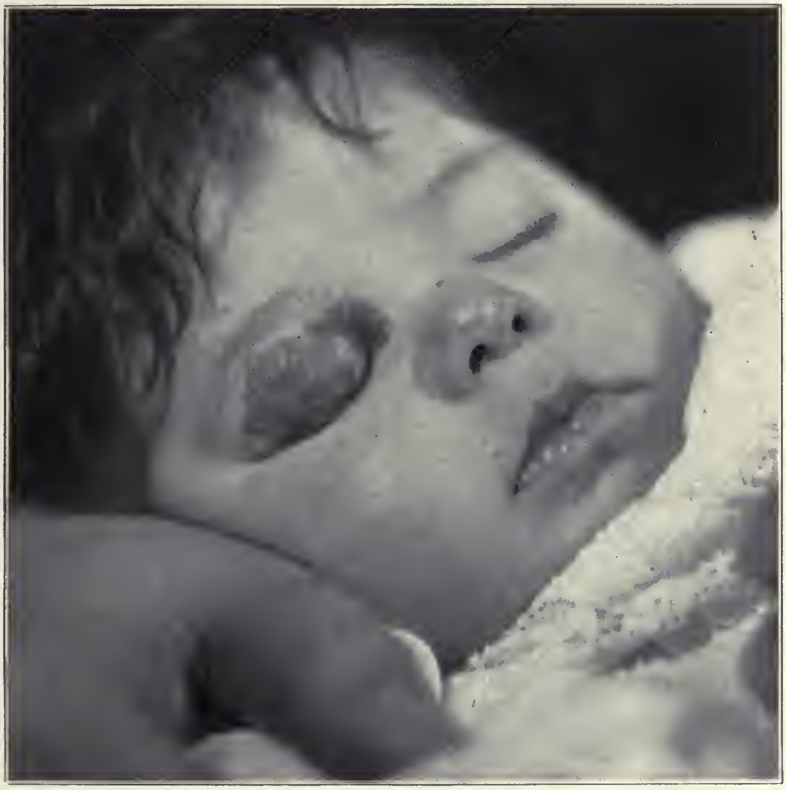


Fig. 1 (E. S., aged 1 year).—Hemangioma of the upper lid, the size of a quarter; raised, bright red in color. The child is unable to elevate the lid.

Several patients are still under treatment and are making satisfactory progress. In completed cases the average number of treatments given was fifteen; the average interval, twenty-four days, and the average dosage in milligram hours, 40. The average distance between the radium and the skin was one-fourth inch. When erythema or crusting has followed treatment, it has been attributed to too short a distance from the skin, rather than to the amount of radium used or the duration of the treatment.

The angiomas varied in size from that of a dime to that of the palm; most of them were raised above the skin level, some as much as 1 cm. Eight of the lesions had ulcerated before the patients came for treatment. Of these patients three had had spontaneous hemorrhages.

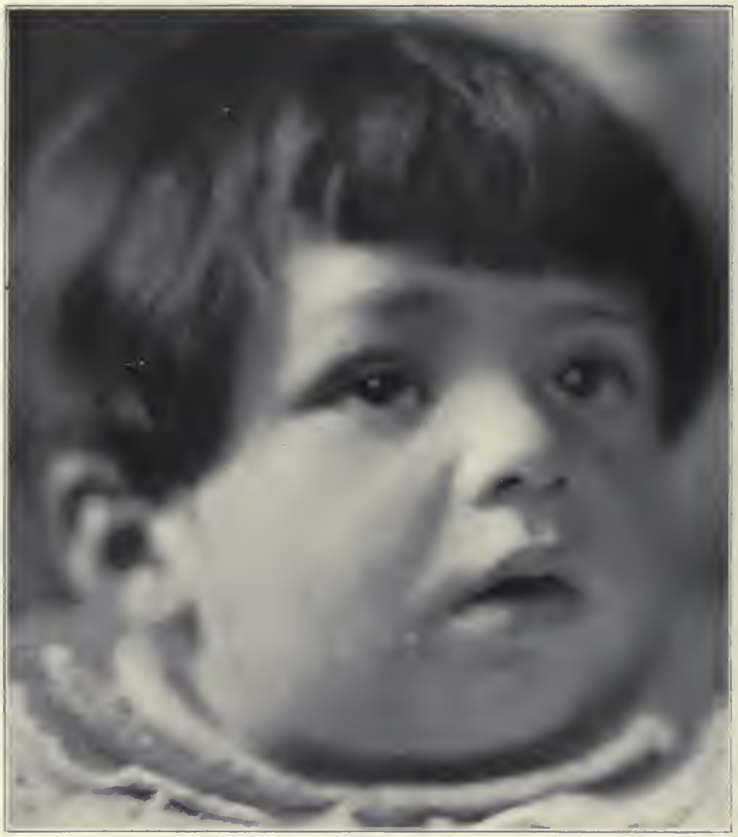


Fig. 2. (E. S.).—Nineteen months later, after twenty-one applications of radium; total milligram hours, 333; average dose, 28 mg. hours; slight superficial ulceration at first period which healed in one month. Result of treatment excellent; no red areas remaining; lid now has perfect function.

One case had previously been treated with carbon dioxid snow with some slight improvement. The remaining cases were uncomplicated. The average age of the patients at the beginning of treatment was 14 months. The most rapid and satisfactory results were obtained in the younger children.

No attempt will be made to record in detail the results obtained, since the number of cases treated is not sufficiently large to justfy any conclusions. The end-results are always a matter of personal opinion, and the possible results by other methods of treatment are always open to argument.

The fact that most of these patients remained under treatment for periods of from six to eighteen months justifies the belief that the parents were satisfied with the progress made and were willing to spend the time and effort involved in keeping appointments rather than in seeking more rapid methods of treatment. Several illustrations with notes on the treatment give a fair idea of the end-results in certain favorable cases. Photographs are not entirely satisfactory records of the progress of these cases because of the difficulty of making red register at its proper value on ordinary photographic plates.

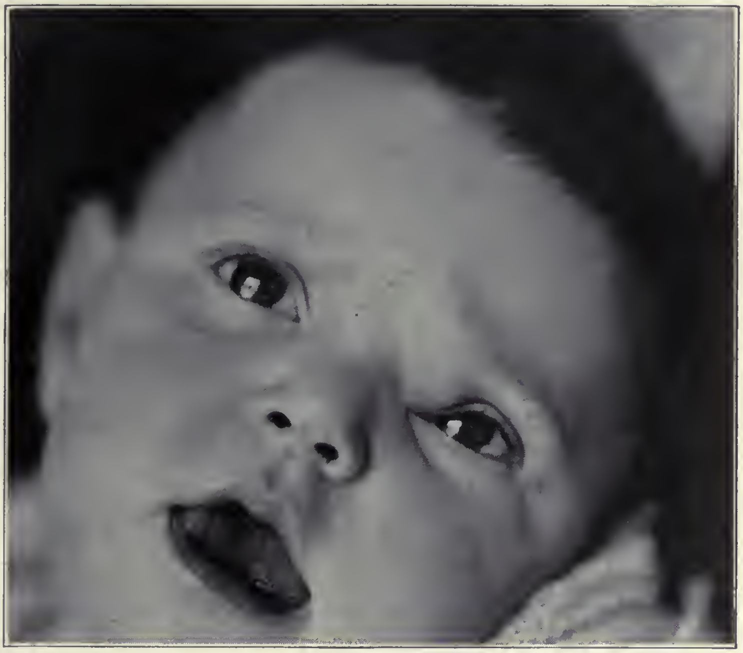


Fig. 3 (V. H., aged 9 months).—At birth a small bluish area was noted on the inner angle of the uper lid; this became progressively larger and began to swell at the age of 4 months. When the radium therapy was begun the tumor was 1 cm. in depth and width.

COMMENT

A fairly uniform experience warrants the generalization that, other things being equal, the younger the patient, the better and more rapid are the results under radium therapy. This point needs emphasizing because of the general practice of physicians of advertising postponement of treatment until the child has at least reached school age. Angiomas are much more refractory in adults than in children. In the former, they are really organized tumors. Healing can be obtained only by combining the specific effects of radium with its destructive properties.

Another point that should be noted is the following: The presence of ulceration and hemorrhage is not a contraindication to the use of radium. Ulcerating and bleeding areas healed with remarkable rapidity after one or two such treatments. In the cases in which overtreatment produced exulcerations, no hemorrhages were noted, and the areas healed without local applications and practically without scarring.

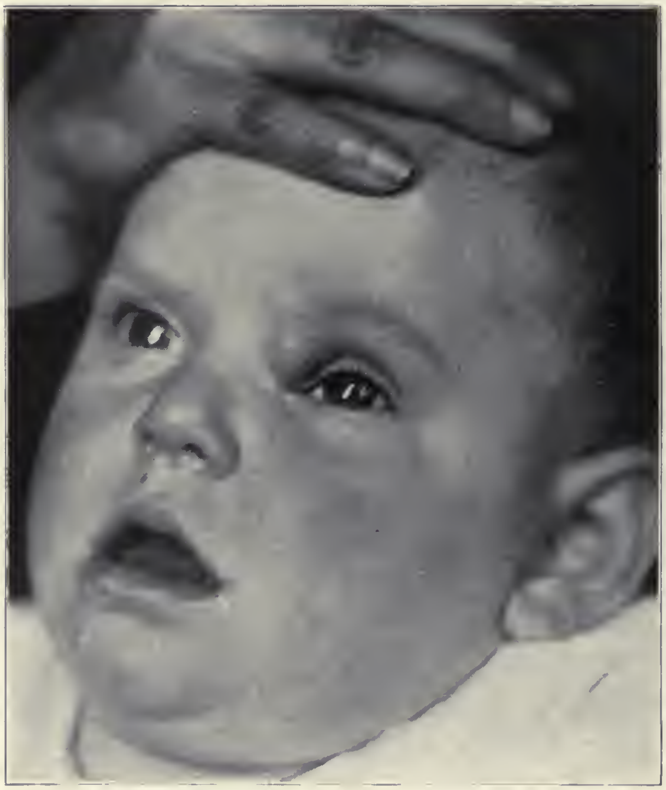


Fig. 4 (V. H.).—Same patient as in Figure 3, after three applications of radium.

In the therapy of vascular nevi, a fairly wide range of selection is open to the physician: surgery, the electrolytic needle, electrocoagulation, carbon dioxid snow, caustics, ultraviolet light, roentgen rays and radium. These have all been used with varying degrees of success, depending on

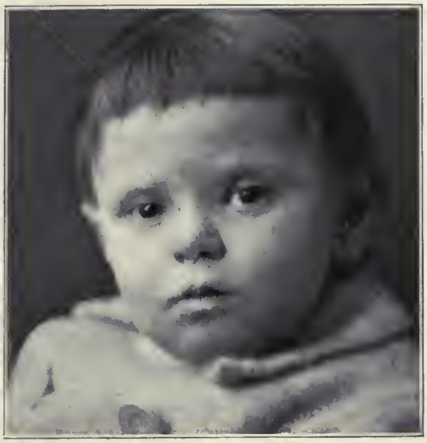


Fig 5 (V. H., aged 20 months).—After seven applications of radium.

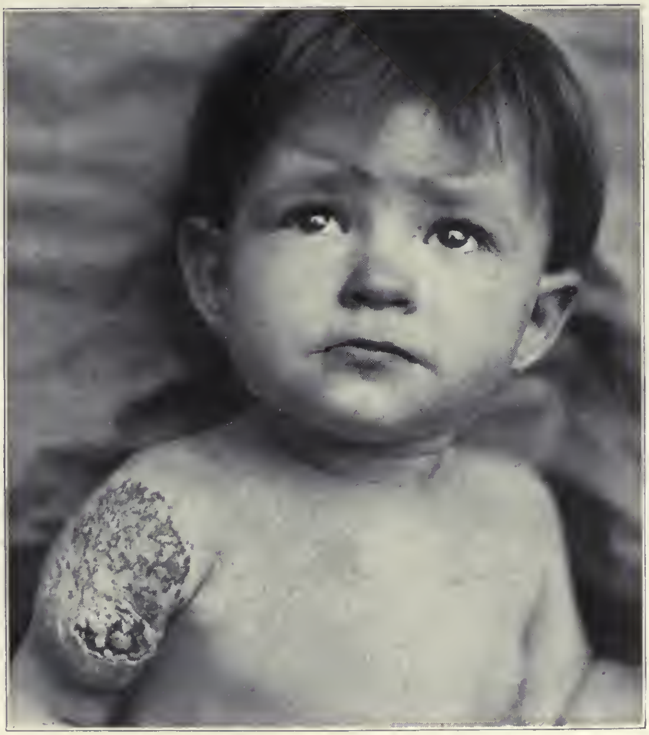


Fig. 6 (A. L., aged 1 year).—Before begining radium therapy. Tumor is elevated 2.75 cm. above the surface of the arm. Tortuous vessels may be seen which extend to a point, 4 cm. from the right sternal border. The tumor is broken down at the lower inner quadrant. The mother states that it has broken down and discharged on several occasions.

the location, type and size of the nevus and upon the skill of the operator. Since this type of new growth rarely endangers life, the problem becomes one of obliterating the abdominal blood vessels with the least possible damage to the surrounding tissues and the best cosmetic result, due regard being had to the amount of discomfort caused, the time consumed and the expense involved.

A skilful surgeon can remove small nevi in favorable locations with surprisingly insignificant scars. This method has the advantage of completing the eradication of the growth at one operation. There are certain disadvantages.

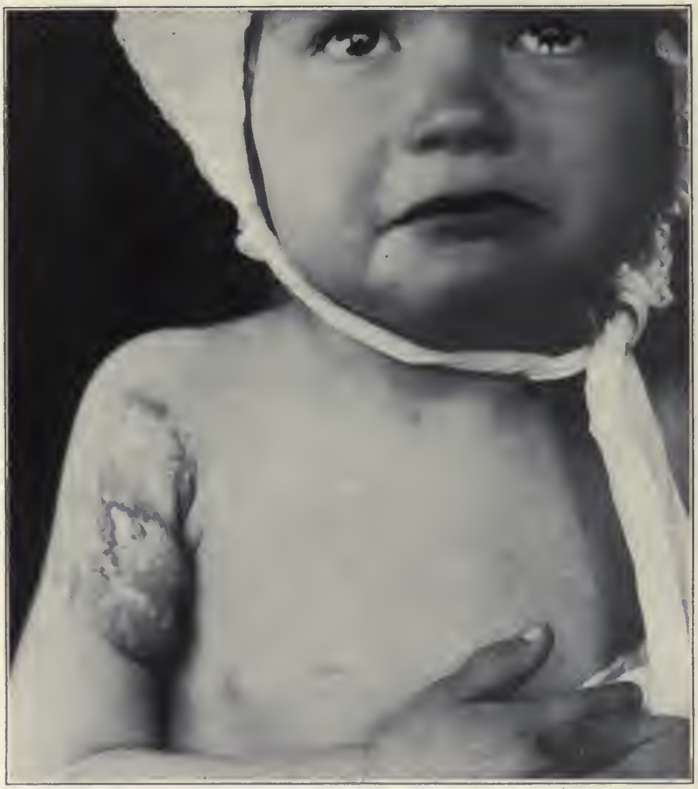


Fig. 7 (A. L.).—Same patient as in Figure 6, after fourteen treatments with radium.

There is always a possibility that the growth may recur if all the abnormal vessels are not removed. Keloids may develop in the scar. Infection, with failure of primary union and a more unsightly scar, may occur. If the lesion is extensive, secondary skin grafting may be needed, and, even with an excellent take, from the surgeon's standpoint, the cosmetic effect and sensory result may not be satisfactory.

In our experience, if the lesions are on the face or in regions where the skin is tightly stretched or if they involve an extensive area elsewhere on the body, particularly if there is involvement of blood vessels surrounding the lesion, the surgeon of long experience is quite likely to decline to attempt the removal of these growths.

The electrolytic needle is the method of choice in the treatment of spider nevi and telangiectasia in general. When used on the larger growths, much depends on the skill of the operator. There is usually some scarring. In any case it is almost impossible to obtain a uniform effect over an area larger than the end of a lead pencil, and, when used on larger lesions, an unpleasant mottling is likely to be the end-result. The treatments are painful and time consuming.

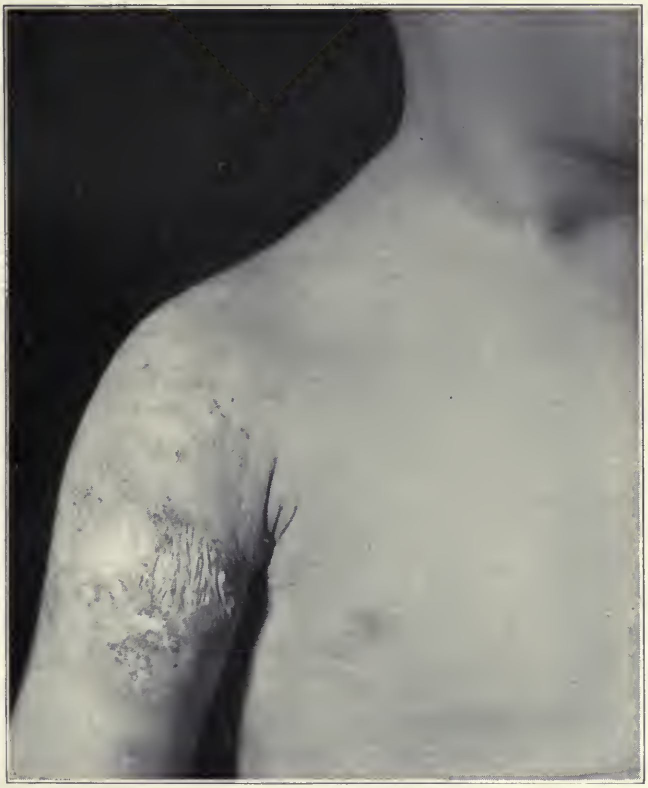


Fig. 8 (A. L., aged 2½ years).—Same patient after twenty-one treatments with radium; no discharge since treatment was instituted. At the distal end, angleworm vessels are still present. At the middle third, there is an area of skin resembling cigaret paper resulting from overdosage. The tortuous vessels previously present on the chest have entirely disappeared.

Electrocoagulation is one of the newer methods of treatment and has much to commend it. Few men have had enough experience with it to use it successfully. In any case it involves the ability to determine in advance the limits of the growth, and this in certain cases offers a difficult problem. If it were possible to locate the main vessels supplying the nevus and obliterate them by this method, it is conceivable that a perfect result might be obtained.

For the cavernous types of angioma of moderate size with a hard background, such as the bones of the skull or any other bony background or even firm muscle that exerts counter pressure, carbon dioxid snow is probably the method of choice. The operation in itself is usually a painful procedure, and in certain cases marked constitutional disturbance may persist for several days following its use. If the time and pressure factors are properly estimated, an excellent result may be obtained. The use of carbon dioxid snow presupposes the necessity of destroying the covering of the blood vessels and replacing it with scar tissue. When the nevus is too large to be covered at one application, the possibility of uneven treatment or of overlapping treatment must be borne in mind.

The use of caustics, either acid or alkaline, is becoming less common. The method has no advantages over other forms of therapy, and sometimes unsightly scars result.

Treatment of port wine marks by the use of the Kromayer lamp has given good results in the hands of a few, expert in its use; most patients become discouraged because of the large number of exposures required and the slow improvement observed.

The treatment of vascular nevi by means of the roentgen ray is no longer in vogue. While most clinicians are inclined to believe that the same effect can be produced with the roentgen ray as with radium, these vascular new growths are a stumbling block in the way of a sweeping generalization, for their response to radium is much more prompt and complete. The roentgen ray is known to have a selective action on lymphoid tissue; apparently radium has, in addition, a selective action on the vascular endothelium of these nevi which the former does not possess.

Pinch[1] gives the following explanation of the action of radium on vascular tumors:

> Prolonged intensive radiation of blood vessels with radium is productive of proliferation, vacuolation, and degeneration of the endothelial cells, with leukocytic infiltration of the walls, and subsequent distortion of their caliber.
>
> If, however, the radiation be of mild degree, acting for but a short time at prolonged intervals, multiplication of the endothelial cells with increased fibrosis of the vessel walls occurs. These changes result in a definite narrowing, perhaps even obliteration of the lumen of the smaller vessels and it is in this fashion that the cure of angiomas is induced.

---

[1] Pinch, A. E. H.: A Report on the Work Carried on at the Radium Institute, London, from Jan. 1, 1920, to Dec. 31, 1920, Radium **17:**192 (Sept. 6) 1921.

The skin over angiomas of the type under discussion is rarely normal. In certain subcutaneous forms and in some lymphangiomas the skin is not abnormal, and it is possible to cause their regression without appreciable damage; but in the reddish or violaceous lesions, the skin is definitely thinner and more fragile than normal. The sebaceous, sweat and hair glands are scanty or absent, and even if the afferent blood vessels are ligated or destroyed by an electric current or heat, so that the nevus is obliterated, the remaining covering will not approximate normal skin. Therefore, it is evident that a perfect cosmetic result is not possible and that the method of choice is either surgery or some other form of treatment that will destroy the overgrowth of blood vessels, with a minimum of damage to the delicate overlying structures.

SUMMARY

In our experience the disadvantages and advantages of radium in the treatment of these angiomas are these: Radium therapy is expensive and time consuming—both because of the necessity of individual treatments and because of the long intervals between treatments. There is also the chance of overtreatment, with subsequent ulcer formation and very tardy healing. The possibility that telangiectasia and an atrophic skin may result, followed later by keratosis and epithelioma, has also to be considered.

The advantages of radium treatment are the freedom from pain, the very gradual changes in the lesion which can be watched from treatment to treatment and the probability of causing the lesion to disappear without appreciable damage to the overlying skin. In addition, there is the advantage of rapid healing of ulcerations and hemorrhagic areas, the absence of scarring, under favorable conditions, or, when scarring is unavoidable, the production of a smooth, supple and comparatively inconspicuous scar. It is possible to treat successfully lesions that, because of their location are not suited to other procedures; for example, nevi of the eyelids, or others on account of their depth and extent. Most potent of all reasons for using radium in treating angiomas is the fact that radium exerts a definite, specific, selective action on the abnormal endothelial cells lining the blood vessels which are at fault in the process. Apparently, this is not true of any other therapeutic agent at our command.

Not all angiomas respond equally well to radium treatment. The port wine mark in very obstinate, since flat nevi generally are more refractory than the raised. Many nevi of small size and situated on covered parts are easily destroyed by more rapid methods.

The scar following the skilful use of carbon dioxid snow is often insignificant. Telangectasia, classed as nevi, is better treated by electrolysis. Surgery often gives brilliant and rapid results.

In certain selected, raised vascular nevi of the face, radium therapy yields results which probably cannot be achieved by other methods. especially if the treatment is commenced in early infancy.

ATRESIA OF THE DUODENUM AND RIGHT INTERNAL HERNIA

REPORT OF A CASE *

JOHN J. MORTON, M.D.
NEW HAVEN, CONN.

The occurrence of congenital atresia along the gastro-intestinal tract is by no means a rare condition, Davis and Poynter [1] having assembled the reports of 392 cases of occlusion between the pylorus and anus. A further analysis shows that the duodenum is the site of predilection, as the lesion was found there in 134 cases of the series.

Right internal hernia, on the other hand, is a condition which warrants report whenever it is found, since Moynihan [2] was able to collect but seventeen cases in 1906, when his classical monograph appeared. Herniation into the infraduodenal fossa, according to this author, is the rarest of all the types of internal hernia. Armand,[3] in his Thèse de Lyon, 1903, reported the only case so far on record.

The subjoined case is presented because of the combination of the two foregoing defects in one individual; because of the rarity of such a finding, and also for the purpose of discussing the associated features of interest to clinicians in making an early diagnosis in such cases.

REPORT OF CASE

History.—A boy, born at full term, May 2, 1922, at 4:20 a. m., with spontaneous delivery, was normal in outward appearance. The following morning he began to vomit a dark brownish material, which appeared to be blood streaked. He had one normal bowel movement. Vomiting continued throughout the day.

Examination.—Dr. Grover Powers saw the baby the following morning. He was small, slightly jaundiced and did not appear to be premature. He looked ill and vomited frequently, the vomitus being a peculiar brownish fluid which suggested a mixture of blood and meconium. Benzidin and guaiac tests of this material were positive. Peristaltic waves were observed moving across the prominent abdomen below the umbilicus, from the left hypochondrium to the right iliac region. Careful examination of the lungs revealed nothing abnormal, the question of diaphragmatic hernia being considered. Dr. Powers concluded that in view of the history and the age of the patient and because of the marked peristaltic waves, the most probable diagnosis was an intestinal obstruction of a congenital nature and the most likely location, the duodenum. He suggested

---

* Received for publication, March 26, 1923.

* From the Surgical Section of Yale University and the Surgical Clinic of the New Haven Hospital.

[1] Davis, D. L., and Poynter, C. W. M.: Congenital Occlusions of the Intestines, Surg., Gynec. & Obst. **34**:35-41 (Jan.) 1922.

[2] Moynihan, B.: On Retroperitoneal Hernia, New York, 1906.

[3] Armand, Cited by Moynihan (Footnote 2).

a duodenal atresia as the cause; but from his findings, especially the location of the peristaltic waves, he could not be sure that the obstruction was not lower down in the intestinal tract.

Dr. Edwards Park, who later saw the baby, felt that there was a duodenal atresia. He cleared the question of the nature of the peristaltic waves by the introduction of water into the stomach, which demonstrated conclusively that this organ was unusually dilated and extended as far down as the brim of the pelvis. After water had been introduced, there was a marked succussion sound over apparently the entire abdomen. Another point of interest was that the stomach tube could be plainly felt through the abdominal wall below the umbilicus. This was very easily demonstrated when it was partially withdrawn. By forcing air into the stomach its dependent position and great dilatation could be made out.

The report of the roentgen-ray examination made by Dr. Scott, after barium had been introduced, was as follows: "Plate and fluoroscopic examination of the stomach shows a well marked definite and total obstruction in the duodenum, approximately 2 cm. from the pyloric opening. Practically no barium sulphate passes this point in thirty minutes times". (Fig. 1).

The patient was seen in consultation by Dr. Morton, who concurred in the diagnosis and performed an exploratory laparotomy a short time later.

Diagnosis: Congenital obstruction, second portion of duodenum.

Operation.—May 22, 1922, a split right rectus incision was made under procain anesthesia. When the peritoneal cavity was opened, a very large liver appeared, the lower edge of which was at the level of the umbilicus. Accordingly, it was necessary to enlarge the incision downward to the right of the stump of the umbilical cord. When the liver was retracted upward, a large dilated stomach was encountered with a markedly distended loop of duodenum beyond the pylorus. The appendix and cecum had not descended into the right lower quadrant but occupied a position near the gallbladder. The transverse colon was a very narrow strip of bowel adherent to the stomach by a thin veil of tissue. A band consisting of five or six loops of small intestine occupied the right portion of the abdominal cavity, whereas the entire large bowel was present in the left portion, apparently neither the large nor small bowel having rotated completely. Following the small intestine from the ileocecal valve upward, it was observed that about one half of the small intestine remained behind a thin walled pouch on the right side of the abdomen. By gentle traction, the bowel could be seen through this thin layer of tissue unfolding itself and coming out into the open. At one portion about 2 inches of the small bowel was of a purplish color; but when it was released from its abnormal position the circulation quickly returned. By continued traction the entire small intestine was freed. Immediately vigorous peristalsis set up in the dilated duodenal loop and air appeared to pass from this portion of the intestine, which became smaller in size. The operator then attempted to find the opening of the hernial sac; but this was not possible as it had collapsed and could not be demonstrated. The small intestine semed to emerge in its normal position at Treitz's ligament, and the obstruction appeared to be relieved.

Closure was made in layers: fine catgut being used for the peritoneum; stay sutures of silkworm gut were introduced; chromic catgut was used for the fascia, fine plain catgut, subcutaneously, and silk for the skin. Before complete closure was accomplished, about 200 c.c. of physiologic sodium chlorid solution was introduced into the the peritoneal cavity.

The patient stood the operation well, lying quietly on the table with no struggling throughout the procedure. His condition on return to the ward was practically the same as before operation.

Course.—Following the operation, he received 30 c.c. of citrated blood into the longitudinal sinus in order to combat the melena neonatorum. Small amounts of water and breast milk to which sugar was added were given during the subsequent twenty-four hours. The child vomited a little during the first twelve hours after the operation. As time went on, however, he began to vomit more, the vomitus consisting of a frothy blood stained fluid. Dr. Powers, who was again called in consultation, considered that the baby had pulmonary edema. Death ensued at 6:30 p. m., May 23, 1922.

Necropsy.—This revealed a few patches of bronchopneumonia, but little else of interest except the abdominal condition.

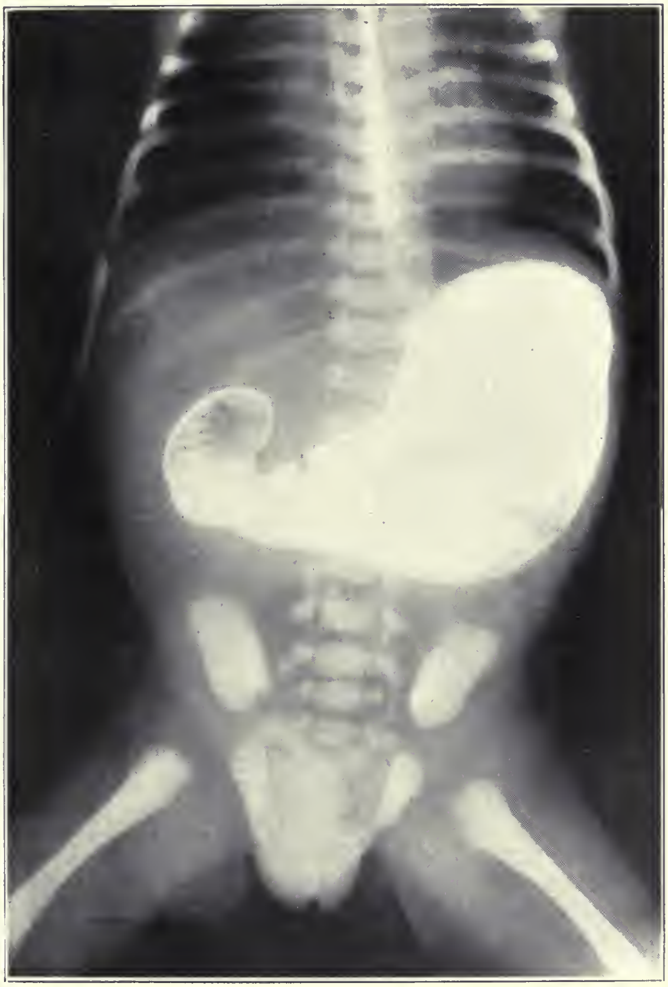


Fig. 1.—Hugely dilated stomach, pyloric constriction and dilated loop of duodenum revealed by barium sulphate meal.

Because of the history the abdominal organs were carefully examined in situ. The stomach was greatly dilated with gas. This dilatation extended into the first part of the duodenum and then abruptly stopped, and no gas could be forced beyond this point. The small intestine was pale in color and appeared entirely collapsed. A careful search was made on the right side of the abdomen for the hernial sac which had been discovered at operation. Several rather loose bands of peritoneum were found, but no definite sac. There was a wide peritoneal band which ran from the colon across the posterior abdominal wall and was attached along the anterior surface of the kidney. Just above the lower pole of the kidney this fold ended, and there was an opening which led between the two peritoneal layers of this band. This probably represented the sac found at operation. Because of the obstruction in the duodenum at about the level of the ampulla of Vater, liquor formaldehydi was injected into the stomach in an attempt to find whether there was a small lumen through which fluid could be made to pass under pressure. No fluid went through. In the same way, liquor formaldehydi was injected under pressure through the duodenum, but it did not pass into the stomach. The abdominal organs were removed as a whole and allowed to become fixed. When the duodenum was opened, the upper part was found to end in a blind sac which formed the point of obstruction. The intestine below was patent but had no connection with the stomach or upper third of the duodenum. The other organs showed nothing of note, so they were left in situ to preserve the relationship of the hernial sac.

COMMENT

The clinical picture of a day old baby vomiting at intervals throughout twenty-four hours offers a problem for early differential diagnosis, the solution of which may be the means of saving the child's life. The character of the vomitus in the case reported, bile stained and blood streaked, pointed to an intestinal obstruction, high in the gastro-intestinal tract. The conditions most likely to be responsible for such an obstruction are stenosis, atresia or internal hernia. Hypertrophic stenosis of the pylorus was ruled out in this case by the fluoroscopic examination of the barium sulphate meal, which demonstrated that the opaque medium passed through a normal pyloric ring into a dilated duodenal loop. It is interesting that such well marked peristaltic waves were present in the stomach, though this finding has been noted in other cases of atresia of the intestine. Tumor of the pyloric region, which could not be palpated in this child, has also been described and has served to make the differential diagnosis more difficult. The presence of a markedly dilated stomach was very clearly demonstrated by Dr. Park on introducing water through a stomach tube, a method easily available to any practitioner, giving an accurate outline of the stomach in relation to the other viscera. The dilatation of the stomach, the peristaltic pattern and the early vomiting, all favored an obstruction, and the fact that no barium sulphate passed a point 2 cm. from the pyloric end indicated that it was complete. Bile in the vomitus has been reported even when an atresia has been present above the ampulla, owing to the presence of an accessory bile duct (Cordes [4]) ; it has also been found in the feces in several cases in which the atresia was below the opening of the common duct. The argument advanced for these cases is that the occlusion could not have become complete until sometime after the establishment of bile secretion. This begins normally in the third month.

---

4. Cordes, L.: Congenital Occlusion of the Duodenum, Arch. Pediat. **18**: 401-424 (June) 1901.

From an operative standpoint, the features of interest were the ease of exploration under procain anesthesia and the numerous evidences of developmental anomalies. These were manifested in the position of the cecum and appendix in the neighborhood of the gallbladder (deficient migration); the attachment of the omentum along the entire colon; the failure of complete rotation so that the ileum entered the cecum from the right instead of from the left; the hugely dilated stomach and duodenum, and the presence of an internal herniation of about half of the small intestine to the right of the median line. The anomalies of migration, descent, etc., have been admirably summarized and presented by Harvey.[5] The hernia occupied a position bounded roughly by the

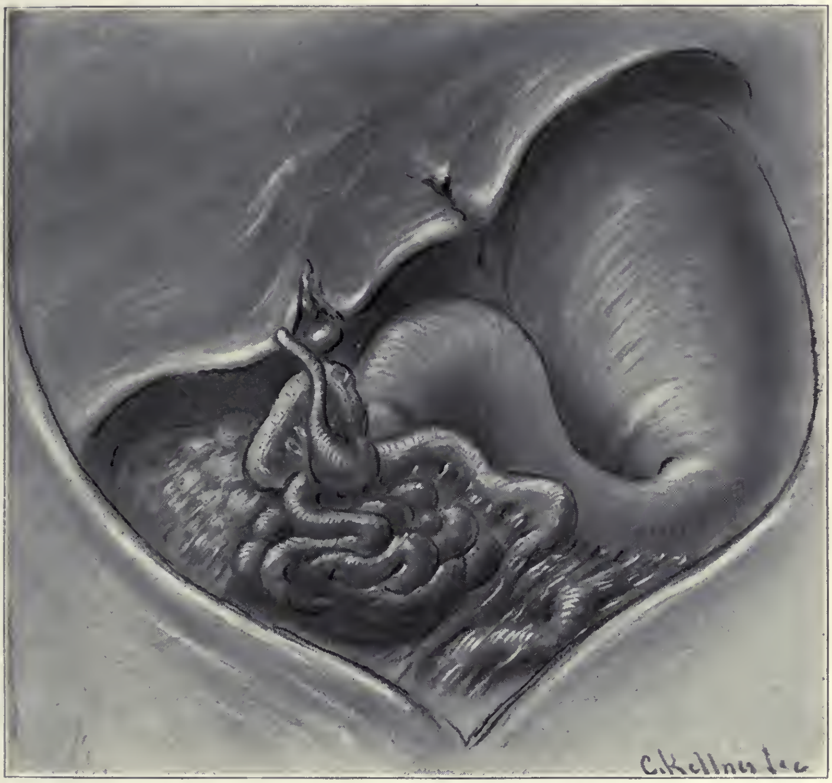


Fig. 2.—Relationship of organs found at operation: large stomach and duodenum, cecum and appendix in the region of the gallbladder, the ileum entering the cecum from the right side, and the herniation of a portion of the small bowel through a thin walled peritoneal sac.

---

[5] Harvey, S. C.: Congenital Variations in the Peritoneal Relations of the Ascending Colon, Caecum, Appendix and Terminal Ileum, Ann. Surg. **67**:641-686 (June) 1918.

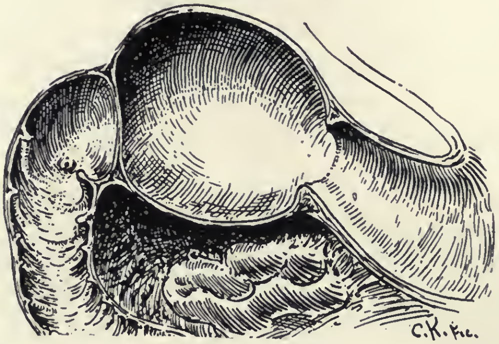


Fig. 3.—Cross-section showing the diaphragm across the duodenum above the papilla of Vater.

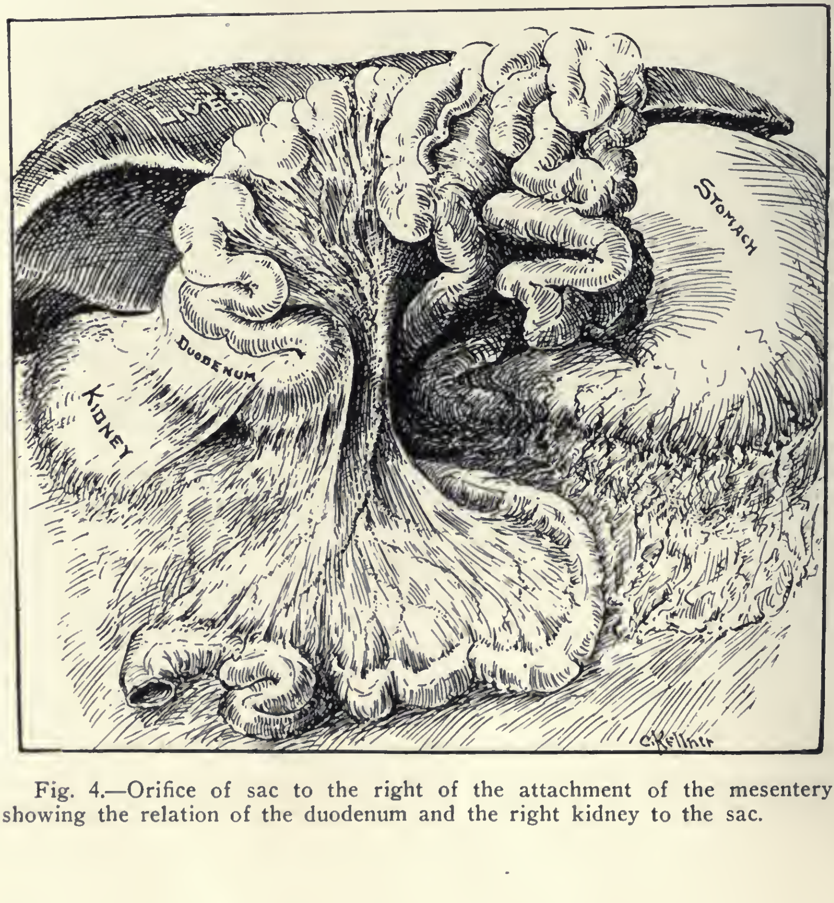


Fig. 4.—Orifice of sac to the right of the attachment of the mesentery, showing the relation of the duodenum and the right kidney to the sac.

right kidney, inferior surface of the liver and the second portion of the duodenum. There was a filmy veil of tissue through which the small bowel was easily seen uncoiling and coming into the open on gentle traction (Fig. 2). On complete reduction vigorous peristalsis started up in the released intestine and, to all present at the operation, the dilated duodenum and stomach appeared to become smaller so that the cause of the obstruction was believed to be removed. The only way that the operator can account for this observation is that considerable pressure was exerted upward to draw the large liver and dilated stomach out of the field. This may have emptied the air from the stomach through the mouth. Necropsy showed that there was an unbroken diaphragm across the duodenum above the ampulla (Fig. 3) so that there could have been no passage of material into the intestine

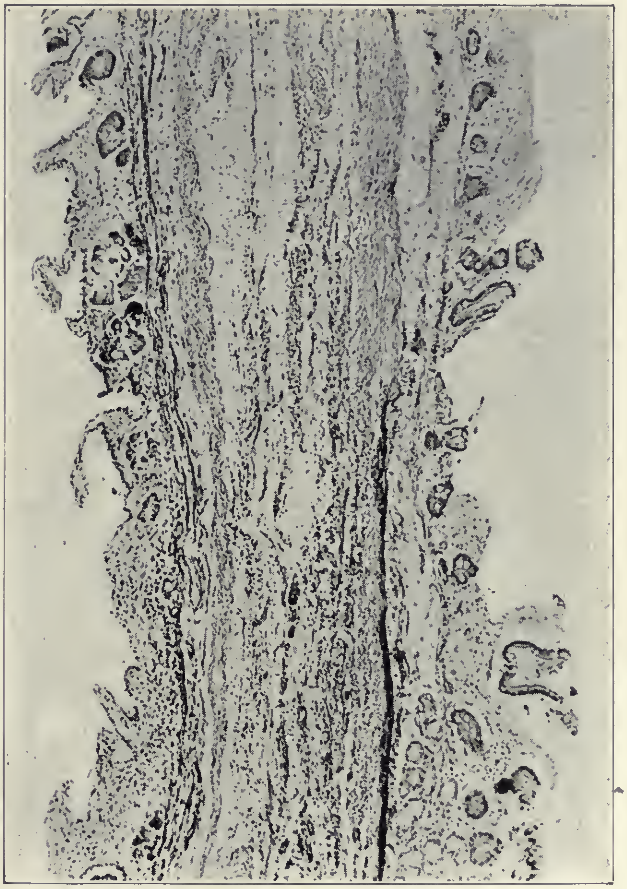


Fig. 5.—Microscopic section of membrane across the duodenum, showing the mucosa on each side, glands, submucosa and intestinal villi.

from above this point. The greatest interests centers in the location of the hernial sac. It was very difficult to find the opening at necropsy; but it was finally demonstrated as a fold of peritoneum bridging the space, from the second portion of the duodenum to the lower pole of the right kidney. In this situation, the opening looked downward and to the left. There was no vessel of any kind in the reflected edge of peritoneum, a fact which is incompatible with the ordinary type of right internal hernia described by Moynihan.[2] This type requires either the superior mesenteric artery or its continuation, the ileocolic in the anterior margin of the sac. The description fits more nearly that of the infraduodenal fossa described by Armand,[3] in that the anterior boundary of the sac did not contain a vessel. It differs in one particular, however, namely that the orifice was situated to the right of the attachment of the mesentery, whereas in Armand's case it was to the left of this structure (Fig. 4).

A possible explanation of the occurrence of such a hernial sac lies in the fact that the posterior layer of the mesentery of the duodenum normally becomes fused to the posterior abdominal wall in the third month and loses its identity. Failure to undergo this fusion would leave a space much the same as that under discussion.

In regard to the surgical procedure to be used in an atresia of this kind, it seems to me that an incision parallel to the long axis of the affected bowel crossing the diaphragm, with complete removal of the membrane and suture of the incision transversely, as in a Heineke-Mikulicz pyloroplasty, would be the operation of choice. The two successful operations on record for atresia consisted in gastro-enterostomy and duodeno-entero-anastomosis.[6] These elaborate operations are absolutely essential for some cases; but, when there is an obviously patent lumen both above and below the point of obstruction, the danger of infecting the peritoneum is so slight in the upper intestine that an exploration of the obstructed site would seem indicated. In this way a simpler operation might be performed.

Microscopic section of a portion of the membrane showed normal mucosa and glands on either side. Villi were also well developed and a submucosa backed up to a similar layer with intervening loose areolar tissue (Fig. 5).

---

6. Schroder, C. H.: Congenital Obstruction of the Duodenum, J. A. M. A. **78**:1039-1041 (April) 1922.

MYELOGENOUS CHLOROMA

REPORT OF CASE WITH NECROPSY *

NATHAN CHANDLER FOOT, M.D.,
AND
GWENDOLYN JONES, M.D.
CINCINNATI

The case herewith reported is of interest, first, because few instances of chloroma are published each year (only three in 1922), and, secondly, because the symptoms in this child all pointed to cerebral lesions and diverted the attention of the clinicians from the underlying condition. No superficial tumors were present, an unusual feature which further added to the difficulties of diagnosis, although the blood smears were typical of acute myelogenous leukemia. It is also interesting to note that the testis and epididymis were invaded by the tumor, these having been reported hitherto as being involved in only one instance.[1] The diagnosis had been abdominal spasms, worms and poliomyelitis before admission to the Cincinnati General Hospital; after admission, it was a question whether the case should be considered lymphogenous chloroma or encephalitis with a severe anemia.

Our knowledge of chloroma dates back to 1854, when it was first described by King,[2] who gave it its name. It was not until Türck's [3] paper appeared in 1903 that a myelogenous, as well as a lymphogenous, type was recognized. This idea was further elaborated by Klein and Steinhaus,[4] and reached its fullest development when Askanazy [1] declared that the majority of, if not all, chloromas were myelogenous. An historical account of the development of the theories concerning the disease will be found in the paper of Rowe and Hirschboeck.[5] More elaborate discussions in German are those of Fabian,[6] Roman [3] and Askanazy.[1]

---

* Received for publication, April 9, 1923.

* Read before the Cincinnati Academy of Medicine, April 16, 1923.

* From the Departments of Pathology and Pediatrics, University of Cincinnati College of Medicine and Cincinnati General Hospital.

[1] Askanazy, M.: Beitr. z. path. Anat. u. z. allg. Path. **63**:22, 1917.

[2] King: Month. M. J. **2**:385, 1854.

[3] Türck, cited by Roman, B.: Beitr. z. path. Anat. u. z. allg. Path. **55**:61, 1913.

[4] Klein, K., and Steinhaus, J.: Zentralbl. f. allg. Path. u. path. Anat. **15**:49, 1904.

[5] Rowe, O. W., and Hirschboeck, F. J.: Myeloid Chloroma, Am. J. Dis. Child. **24**:239 (Sept.) 1922.

[6] Fabian, E.: Beitr. z. path. Anat. u. z. allg. Path. **43**:172, 1908.

As outlined by Ewing,[7] chloroma may be divided into two types, lymphogenous and myelogenous, of which the former is more common. It occurs chiefly in young males, averaging 18.8 years of age; runs an average course of 5.5 months' duration, and terminates fatally. It appears principally in the ribs, dura, dural sinuses, sphenoidal and ethmoidal sinuses, ear, nose and throat. It often invades the sternum, vertebral column, pelvic bones and occasionally the long bones. In such cases, the distinction from myeloma is not clear. The facts that myeloma usually occurs in the fourth and fifth decades, rather than in youth, and that the blood picture in that disease is more definitely aleukemic help somewhat in distinguishing the two conditions. In myeloma there are Bence-Jones albumoses in the urine, while in chloroma there are not. Chloroma involves the lymphatic system; the cervical, axillary, mediastinal and deep chains of nodes suffering almost invariably. They have escaped in but one myeloid case. Of the other organs involved, the pancreas, thyroid, thymus, ovaries, mammae, prostate, bladder, testis and epididymis have been described as the site of tumor-like growths. A tendency to infiltrate the tendinous insertions of skeletal muscles has been noted. The color of the tumors is a grass-green, or apple-green; but colorless tumors have been noted by Rowe and Hirschboeck [5] and by Birk, Leber and Wende and Miller (quoted by these writers). When the greenish color is present, it tends to fade after a time, or after fixation; but it can often be brought back by treatment of the tissue with hydrogen dioxid. Its nature has been the subject of much speculation and is still not understood.

The blood picture varies extensively. The lymphatic type shows a lymphocytosis; the myeloid type may show myelocytes, myeloblasts or cells even more primitive than the latter. The number of leukocytes varies from 6,100 in Caronia's [8] case, to 491,000 in Stevens'.[9] A consideration of the leukocyte counts in our case demonstrates that this may undergo wide fluctuations in a given instance, so that one must be very cautious in drawing conclusions from a single example. Ewing says: "The process belongs with the systemic sarcomas of blood-forming organs, affecting primarily either the lymphatic system, or the bone marrow." In discussing a case of lymphadenoid sarcomatosis of the ileum, Warthin [10] pointed out the close relationship between such tumors and the leukemias, which are now considered to be tumors of the blood stream. Chloroma has been known to occur in conjunction with tuberculosis, but there is no evidence that these two conditions are related.

---

[7] Ewing, James: Neoplastic Diseases, Ed. 2, Philadelphia, W. B. Saunders Company, 1922, pp. 363-364.

[8] Caronia, G.: Pediatria **30**:437 (May 15) 1922.

[9] Stevens, quoted by Ewing (Footnote 7).

[10] Warthin, A. S.: Tr. A. Am. Phys. **19**:419, 1904.

The symptomatology of the disease is well summarized by Dock,[11] who says: "Out of the protean symptoms of chloroma cases we can separate three sets of conditions: the mechanical results of the green growths, causing many symptoms, both objective and subjective (exophthalmos, visible tumors, pain, deafness, etc.); the toxic symptoms, such as weakness, fever and emaciation; the blood symptoms, such as pallor, hemorrhages and alterations in the blood itself." As will be seen later, our case presents a syndrome chiefly referable to the second and third sets. The mechanical symptoms were never important, aside from the very misleading cerebral hemorrhage and its sequelae.

Few reports on chloroma have been published recently. Two of the cases reported have been myelogenous in type. The case reported by Rowe and Hirschboeck[5] was that of a child, aged 18 months, who had tumors about the zygomas, and the parotid, submaxillary and submental regions. Their necropsy findings have much in common with ours. The other case reported occurred in a boy, aged 3 (Caronia[8]). The chief interest in this instance is the presence of a nodular spleen, several tumors about the face and scalp and the ingenuity displayed in aspirating parts of the tumor for diagnosis by means of a coarse needle and aspirating syringe. The case terminated fatally, but did not come to necropsy. The blood count showed but 6,100 leukocytes, which is decidedly low.

Of the older articles, three in the German literature are of great value. Fabian[6] gives an extensive bibliography, reports two cases, one of each type, and discusses the disease at length. Roman[3] reports three cases in adults, one of them in "an old man" ("Greis") of 62. He has observed myelocytes in the germinal centers of lymph nodes, particularly in the tonsils, which he interprets as being produced there by metaplasia, as he could find but very few examples of migration into the centers by these cells from the blood capillaries. Our observations do not support this theory. In summing up, he points out the similarity of leukemia and chloroma, and in closing he says: "With the colored, as well as the colorless malignant leukemias, a perfectly typical blood picture is found, the blood picture of leukemia—they are, even to the greenish color, identical processes, but differ on account of their malignancy from simple, hyperplastic leukemic processes. In my opinion, it would be desirable to keep them separate and to reserve the term chloroleukemia only for the green, hyperplastic leukemias."

Askanazy's[1] last paper on chloroma gives an excellent and very complete summary of the history of the development of our knowledge of the disease. He reports one case in which there were nodes in the kidneys, bladder and other organs. The tumor cells formed tumor thrombi in the sinuses of the dura, just as in our case. He considers these thrombi of the utmost importance in the differentiation of chloroma from an ordinary leukemia, a point not stressed by other writers. The bone marrow in his case showed extensive peripheral involvement. The tumor cells did not give the oxydase reaction; but, on account of the activity in the marrow and the lack of lymphogenous hyperplasia, he concludes that it was a myelogenous process. He found four types of crystals in the tumor cells, a fact hitherto and since not noted. There was no sign of hematopoiesis in the liver or spleen. He appears to believe that all cases of chloroma are myelogenous, his reasons being well founded and deserving of careful consideration. The current belief that the bone marrow is "invaded" by large lymphocytes, in the lymphatic type, according to his lights, is erroneous; he believes that the large, lymphocytoid cells found at the periphery of the bone marrow are produced there, rather than that they have migrated from the lymphatic system and are, hence, myelogenous in nature. This concept is borne out in our case; but the myelogenous nature of the process in this instance needs no discussion. In conclusion Askanazy writes: "Chloroma is extraordinarily similar to myeloid leukemia with green tumors, but it is not permissable to group them together until the etiological factor is understood, since noteworthy differences, for example their localization, exist. . . . Chloroma, like leukemia, is as a rule myelogenous. . . . The parent cell of chloroma is a hemoglobin-free member of the myelogenous cell series, or at least lies along the road to the development of the myeloid cell."

---

[11] Dock, George, and Warthin, A. S.: Tr. A. Am. Phys. **19**:64, 1904; Med. News. **85**:971, 1904.

REPORT CF CASE

History.—J. H., a white boy, aged 3 years, was admitted to the pediatric service of the Cincinnati General Hospital, Sept. 22, 1922. Delivery had been normal and at term. He had been breast-fed and had had no contagious diseases. At 1 year of age he was circumcised. The mother was dying of carcinoma of the uterus. The father had had both legs amputated following an accident. A sister, aged 9, and a brother, aged 7, were alive and well. Four days prior to admission the child had a very severe nosebleed. Two days later, while playing, he stooped to pick up a clothes pin and fell into a pile of them that lay on the ground. About five minutes later he was found crying, his eyes rolled upward, his head turned to the left. He continued to cry for about fifteen minutes. Since then he had not uttered a sound. The right arm and leg became paralyzed. Apparently, he had not struck his head. There were bruises on the knees, but nowhere else. The next day he vomited and developed clonic contractions in the lower extremities and abdominal muscles. He became feverish.

Examination.—The boy was poorly nourished, semiconscious and was not aroused by noises. It was not possible to determine whether or not he saw. He cried out shrilly from time to time, as though he was in great pain. There were ecchymoses on both knees. No evidence of a fractured skull could be elicited. The eyelids drooped, the left more than the right. The pupils were equal and reacted to light. The tongue was heavily coated; the tonsils were large and cryptic. There was general enlargement of the superficial lymph nodes. The heart, lungs and genitalia were normal. The liver was enlarged and extended a few centimeters below the costal margin. The spleen was not felt.

Neurologic Examination.—There was almost complete flaccid hemiplegia on the right side of the face, trunk, right arm and leg. Sensory functions were not impaired. The reflexes were normal on the left; there was a double plus biceps reflex and knee-jerk, a positive Babinski sign, and absent cremasteric and abdominal reflexes on the right, with negative ankle clonus and Kernig's sign.

Summary.—The findings pointed to a diagnosis of (1) right hemiplegia, (2) stupor, (3) aphonia, (4) general enlargement of lymph nodes, (5) large, cryptic tonsils.

Course of Illness in Hospital.—During the following two weeks there was a gradual amelioration of the symptoms, with a transient phase of spasticity and some changes in the pupillary reactions. At the end of the week, the child had a severe epistaxis that required packing anteriorly and posteriorly. During the following week the packing was removed several times, but as the bleeding persisted, despite the local application of a hemostatic, it had to be replaced. No bleeding point could be located, nor was any foreign body found. At the end of the week the hemorrhage was controlled, but the tendency to bleed persisted. There was slight oozing from the nares. A transfusion of 80 c.c. of citrated blood was given on the eighteenth day after admission. It was followed on the next day by vomiting, and blood was found by Meyer's test in the vomitus. Another transfusion was given on the twenty-second day, 85 c.c. of citrated blood being administered. The clotting time was then two minutes and fifty-six seconds. The patient's temperature rose to 102 F. after the transfusion, but soon fell.

Four weeks after admission, the boy's color had improved noticeably. By the fifth week, he began to grasp at objects, but developed a clonic twitching of the left arm which persisted for another month, gradually subsiding in intensity. Two months after admission he was talking, gaining in strength and playing with other children. The right pupil was larger than the left, and remained so until the end. Improvement continued up to the eighty-third day, when the patient refused food and was less lively and talkative. Reference to the table of blood counts made in this case reveals that the child had had a remission of the leukemia and was now entering upon another relapse. The temperature remained normal, but he began to vomit, the vomiting becoming projectile in character. The right hemiplegia persisted; the temperature rose to 100 F. About three months after admission, purpuric spots and nystagmus appeared in both eyes. Cheyne-Stokes breathing developed, and the child died.

Laboratory Findings.—Spinal Fluid: This was examined at intervals during his illness, five tests being made. It showed little except a marked increase in the cell count, which rose to 190 shortly before death. The blood Wassermann and Pirquet reactions were both negative. The urine was negative, containing no albumin or albumoses. Blood cultures were sterile. The blood count and results of the differential examination are given in Table. 1 and 2.

Necropsy.—This was performed three hours after death. The body was that of a well built, poorly nourished white boy, apparently about 3 years of age. Rigor mortis and postmortem lividity were absent. Small petechiae were present over the ear lobes, right temple, both patellae and the left forearm. The right pupil was 6 mm., the left 5 mm., in diameter. The teeth, tongue and lips were covered with sordes. The cervical nodes did not seem to be much enlarged.

The liver was about 1 cm. below the costal margin. The diaphragm was at the fourth interspace on the right and at the fifth rib on the left. The thymus was small and shriveled, and of a peculiar apple green color. A few small hemorrhages were found beneath the adventitia of the pulmonary artery and aorta at their origin. The middle lobe of the right lung showed massive areas of hemorrhage, which varied in color from bright red to purple. Both lower lobes showed extensive hemorrhages, particularly at the sharp border of their bases. The tonsils were large, and, on section, they presented the same apple green color noted in the thymus. They were homogenous in texture, and the crypts were large and patulous.

The spleen, liver and gastro-intestinal tract were not particularly remarkable. There were numerous hemorrhagic erosions in the gastric mucosa, with some old, coffee-ground blood adhering to them. All of the mesenteric nodes were enlarged and of the greenish color previously described. The mucosa of the pelvis of each kidney was also greenish, which microscopically was accounted for by diffuse tumor infiltration of the submucosa. On the posterior, inner surface of the urinary bladder, which was otherwise normal in appearance, were

TABLE 1.—*Blood Counts*

Date	Erythrocytes	Leukocytes	Hemoglobin Per Cent.	Temperature F. (Maximum)	Comment
9/22		14,400		99.4	Admitted
9/23	4,567,000	19,200		102.4	
9/24	5,000,000	20,000		105.0	
9/29		16,000		99.2	
10/5	2,352,000	12,400	46	101.0	Epistaxis
10/9	2,400,000	16,400	40	101.0	Epistaxis controlled
10/11	2,000,000	11,600	38	99.6	First transfusion
10/13	3,100,000	11,400	36	99.5	
10/17	2,464,000	8,000	42	99.2	Second transfusion
10/23	3,000,000	9,200	52	98.8	
11/22	4,200,000	8,200	55	98.6	
12/11	5,660,000	40,800	60	99.0	Refuses food, sick
12/19	5,200,000	55,400	86	100.6	Died shortly after
Average	3,632,000	18,692	54	During observation	

TABLE 2.—*Differential Leukocyte Counts* *

Date	Polymorphonuclears Per Cent.	Lymphocytes Per Cent.	Transitionals and Large Mononuclears Per Cent.	Myelocytes and Myeloblasts Per Cent.	Normoblasts	Platelets
9/24	25	22	1	52	3	Dimin., large
10/5	14	46	2	38	6	Dimin., large
10/11	24	63	1	12	1	Much dim., large
10/23	38	50	3	9	0	Dimin., large
11/22	16	75	3	6	2	Incr., smaller
12/13	5	34	1	60	3	Dimin., large
12/19	4	18	0	78	8	Much dim., large
Average	28	44	1.57	36.43	3.3 per 200 cells	

---

* Myelocytes were always scarce and difficult to distinguish in many instances, therefore, they have been grouped with the myeloblasts. Poikilocytosis, anisocytosis, polychromatophilia and basophilia were present in the erythrocytes, the latter only during the last few days of life. The averages in the tables mean little, but they show that the blood never approached normal during the child's stay in the hospital.

several thickened areas of greenish, lobulated tissue, with punctate hemorrhages at their periphery. The testes were slightly enlarged and presented the same greenish hue, but, otherwise, they were not grossly remarkable. In view of the fact that they were almost two-thirds replaced by tumor tissue, as shown later, this was interesting. The bone marrow of the ribs was not particularly remarkable in its appearance, but that of the femur was pale, greenish and homogeneous.

When the scalp was opened, a fairly large hemorrhagic area appeared over the right temporal region below a puncture wound. The dura was adherent to the calvarium over the vertex and necessitated cutting before it could be freed. The brain weighed 1,125 gm. When it was removed, a large hemorrhagic area was encountered in the right parieto-occipital region, measuring 8 by 4 by 4 cm. in extent, which was filled with fresh clots. The walls of this cavity were everywhere shot with small, fresh hemorrhagic areas, like bright red polka-dots. The left hemisphere presented a large area, 8 by 6 by 5 cm. in size, which was completely softened and felt cystic. It was located in the left parietal region, just posterior to the fissure of Rolando. Here the brain tissue had undergone marked softening and was yellow and granular in appearance, with a cyst at the center, which contained turbid, grayish fluid. The margins of the cyst were firm and definitely lobulated. This obviously represented an area of old hemorrhage, followed by absorption and degeneration. The ventricles were somewhat distended, the right containing a small quantity of bloody cerebro-

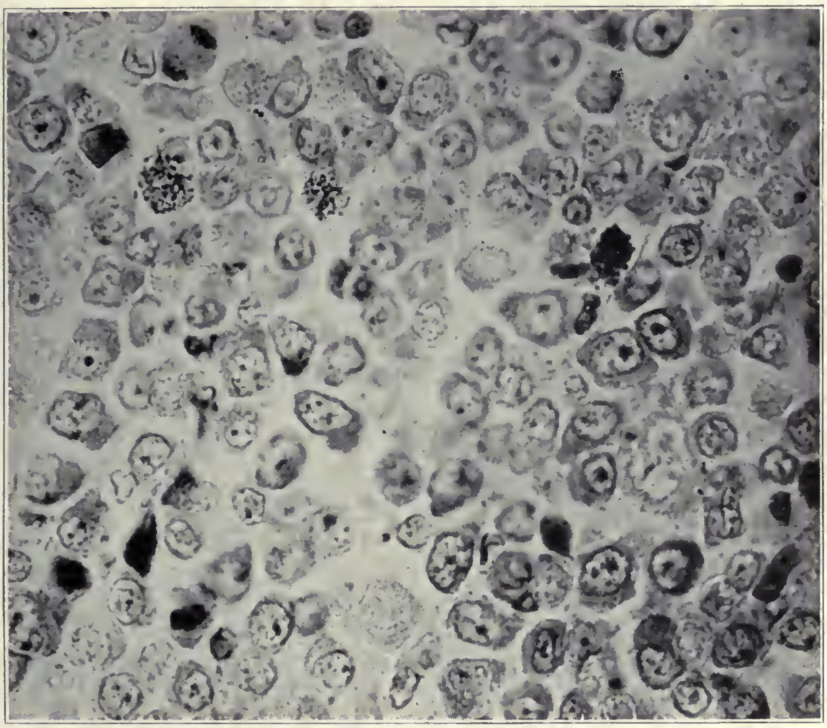


Fig. 1.—Section of femoral bone marrow, Giemsa stain; × 1,000. The heavily stained granular cells are eosinophils. The polygonal outlines of the tumor cells and their prominent nuclei may be noted.

spinal fluid and some blood clots. The meninges, extending from the base and optic chiasm to the cervical cord, were infiltrated generally with hemorrhagic exudate, which also extended upward over the right hemisphere, particularly along the fissure of Sylvius and was marked over the posterior aspect of the cerebellar hemispheres as well. As a whole, the brain was markedly edematous, a large amount of slightly turbid fluid dripping from it.

When the dura was stripped away from the base of the middle fossa, a small, flat mass of apple green, lymphoid tissue was found nestling into the recess at the junction of the petrous and the squamous portion of the temporal bone (tegmen tympani). It measured about 1 cm. in diameter. The torcula contained a mass, which appeared to be a thrombus, rather firm and granular, with masses of greenish tissue at its periphery; otherwise the dural sinuses did not appear to be remarkable.

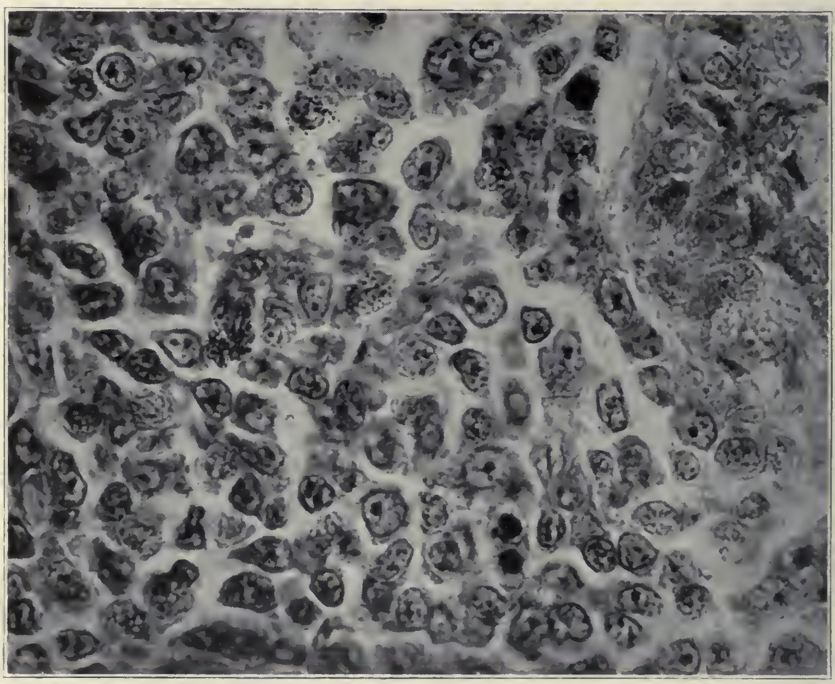


Fig. 2.—Section of testicular metastasis; a portion of a seminiferous tubule at one side; Giemsa's stain; × 1,000.

Microscopic Examination.—Tissue removed at necropsy was fixed in Zenker's fluid and in 4 per cent. liquor formaldehydi and stained with hematoxylin-eosin, eosin-methylene blue and by Giemsa's method, and special stains for oxydase granules were prepared by Graham's alphanaphthol-pyronin and McJunkin's benzidin methods. As the chief pathologic condition encountered in the various organs examined consisted of a tumor and its metastases, we shall consider this phase of the description first.

The tumor was most prominent in the bone marrow (Fig. 1) of the femur and in the testes (Fig. 2), about two thirds of which were replaced by tumor tissue. The cells of the growths showed a variable amount of cytoplasm. Some had but little, others a moderate amount. They measured from 3.75 microns to almost 10 microns in diameter, or if spherical or elongated, the long diameter was about 10 microns, the cross diameter, 5 or 6 microns. The elongated forms were not seen frequently. The nuclei were vesicular, with a very delicate network in which chromatin masses, resembling two or more nucleoli, were suspended. The nuclear membrane was usually distinct; its outline varied from spherical, through ovoid, to reniform, or sometimes it was squash-shaped. The nuclei averaged from 3 to 4 microns in diameter. The cytoplasm varied with the stain used. In the hematoxylin-eosin stain, it appeared vaguely granular, or homogeneous, its color varying from red to deep purple. With Giemsa's stain, tiny neutrophil granules appeared in many cells. Sometimes a few, or many, eosinophil granules were demonstable (Figs. 1 and 2). The cytoplasm was violaceous and homogeneous. In methylene-blue sections, it varied from sky-blue to pink, and the granules were not so evident as in the Giemsa preparations, though they were more evident than in the hematoxylin. Some cells showed spherical masses of a material which stained deep red with eosin, in the Giemsa sections, and appeared to be more or less homogeneous, although granules appeared in it when it was examined with green light. The outline of the cells as a whole was either spherical or ovoid and sometimes angular or polygonal. Oxydase granules were readily demonstrable in the cytoplasm by the Graham and McJunkin technics. The situation of these cells in the bone marrow, where innumerable mitoses were encountered, and the fact that the entire tissue was filled with them, their possession of many or few neutrophil granules and their dissemination in organs not particularly connected with the lymphatic apparatus would alone indicate their myelogenous origin. The positive oxydase reaction appeared to clinch the diagnosis. The bone marrow was unrecognizable as such in the femur, except for the presence of megakaryocytes; that of the ribs showed a subperiosteal zone of metastasis, the marrow of the more central portion being approximately normal. This is interesting in connection with

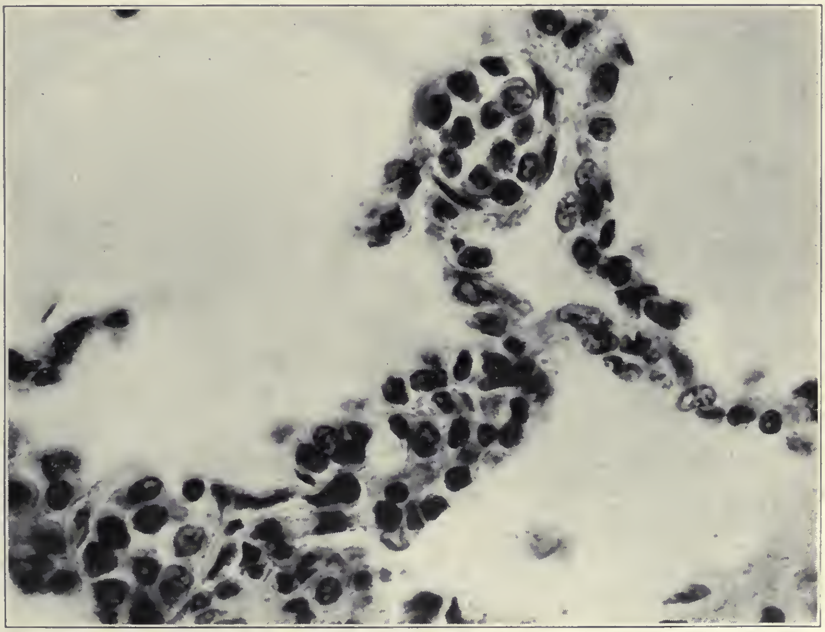


Fig. 3.—Capillary engorgement of pulmonary tissue, walls of alveoli; hematoxylin-eosin; × 800.

Askanazy's[1] observations. The testicular tubules were normal, but so wedged apart by tumor masses that some fields showed only two or three of them. Mitoses were less numerous in the metastases than in the bone marrow, which appeared to contain the primary tumor.

Some lymph nodes showed infiltration by the tumor, and some were wholly free from it. Several nodes were examined, and it was found that they were as often uninvolved as involved. The lymphoid centers in the nodules were quiescent, or sclerosed and "exhausted." There was no evidence of lymphoblastic activity, nor of myeloid metaplasia. If they contained any myelocytes, these were usually directly outside capillaries and probably migrated through their walls. A careful search was made for any such metaplastic centers as Roman describes, but without success.

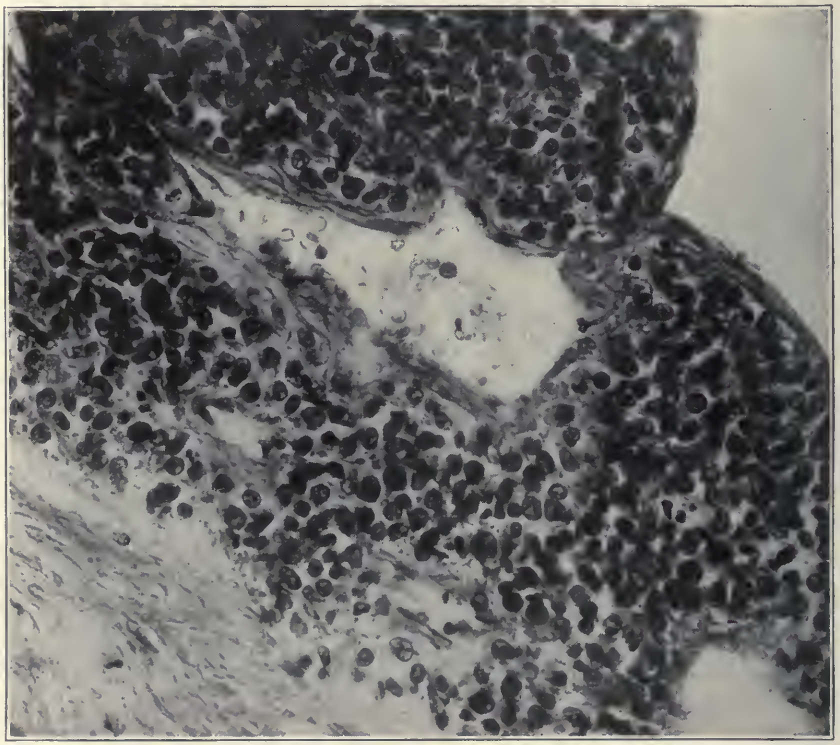


Fig. 4.—Dural metastasis, from wall of a sinus, hematoxylin-eosin; × 800.

The tonsils showed infiltration at the base, near the capsule, but the lymphoid apparatus was not directly involved.

There were small, focal metastases in the heart muscle, near vessels, but they were nowhere extensive.

The lungs showed thickening of the alveolar walls, and their vessels, from capillaries to large arteries, were filled almost completely with tumor cells (Fig. 3), very few erythrocytes being present (Compare Rowe and Hirschboeck[5]). The hemorrhages seen at necropsy were found microscopically.

The liver sections were practically negative.

The topography of the spleen was well maintained. The malpighian corpuscles were readily distinguished by their lymphoid tissue, the "germinal centers" of which were reduced to mere masses of sclerosed reticulo-endothelium in which ameboid endothelial cells and much nuclear débris lay enmeshed. The surrounding lymphoid tissue showed no lymphoblastic activity. The sinuses were well defined; the walls were somewhat thickened and contained a moderate number of discrete tumor cells.

Aside from tumor metastases scattered along the pelvic submucosa and the course of some of the larger vessels, the kidney sections were not remarkable.

Sections of the dural sinuses and thrombi showed massive infiltration with tumor tissue, growing just beneath the intima (Fig. 4, compare Askanazy[1]).

Preparations from the margin of the cerebral hemorrhages showed these and, in addition, numerous tumor thrombi that blocked the smaller vessels in the brain tissue and undoubtedly caused the hemorrhages that killed the child, after bringing about hemiplegia. Often such thrombi were surrounded by extensive areas of red cells and necrosed cerebral tissue. The older hemorrhage showed the typical picture of necrosis and was filled with many endothelial phagocytes.

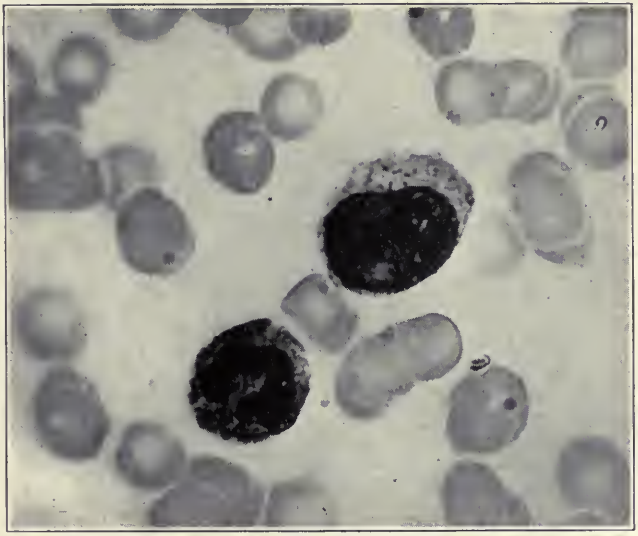


Fig. 5.—Myeloblast and polymorphonuclear from smear of Nov. 24, 1922. A few granules are present in the myeloblast; Wright's stain; × 1,200.

The anatomic diagnosis was: diffuse meningeal and deep cerebral hemorrhages, partial sinus thrombosis at torcula, cardiac dilatation, pulmonary hemorrhages, atrophy of thymus, tonsillar hypertrophy, and passive congestion of liver; chloroma, with metastasis to lymph nodes, tonsils, thymus, dura, cerebrum, pelvis of kidney, testis, urinary bladder and probable primary site in femoral bone marrow.

The microscopic diagnosis was myelogenous chloroma, with metastasis to the organs noted above.

Blood Examination.—As shown by Table 2, a number of smears were made during the child's stay in the hospital and stained by Wright's method. There were always a great many large cells, with a striking superficial resemblance to lymphoblasts. Granules could be discovered after a careful search with a good oil-immersion lens particularly in the early smears (Fig. 5), before the bone marrow had sacrificed quality to quantity, as it did later in the disease. The granules were usually neutrophil, sometimes the cells appeared to be myelocytes with many small granules in a pinkish cytoplasm, more frequently they were myeloblasts with a few small granules of a pinkish cast in a bluish cytoplasm. A few basophilic myelocytes were found. Polymorphonuclear neutrophils were present in moderate numbers; eosinophils were very scarce, none being found in the average count. The lymphocytes were not remarkable. As the disease progressed, the myeloblastic type became almost the sole leukocyte in the field. These cells lay in groups of four or five (Fig. 6). They became less granular and more vacuolated, their nuclei becoming more diffusely and lightly stained. Apparently, the hematopoietic activity of the marrow had reached a point where the myeloblasts were being cast forth in a progressively less mature condition. The erythrocytes showed the changes usually seen in such conditions, poikilocytosis, anisocytosis, polychromatophilia and, as death approached, basophilia. Megaloblasts and normoblasts were present. The platelets were generally larger in size and fewer in number than under normal conditions.

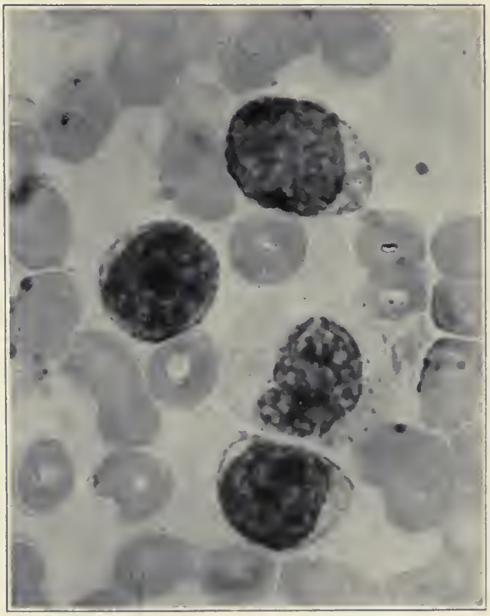


Fig. 6.—Three myeloblasts and a myelocyte from smear of Dec. 29, 1922; Wright's stain; × 1,200.

CONCLUSIONS

We have been unable to find any of Askanazy's crystalline substances in the tumor cells. The fact that he alone of a large number of investigators has found them is not particularly in favor of their being of any great diagnostic importance, or of constant occurrence. One cannot help believing that they may have been artefacts. Roman's myeloid metaplasia of the lymphatic "germinal centers" also stands unconfirmed. The presence of a few myeloid cells in this situation is no more significant than their appearance in the liver sinusoids, or the cellular spaces of connective tissue.

In closing, we must express our unwillingness to consider chloroma as an entity. It is merely a phase of a leukemia, in this case myelogenous in character. The term "chloroma" is useful as indicating the tendency of such leukemias to form green metastases to tumor tissue, as opposed to mere infiltration of the tissues with myelocytes or myeloblasts; just as one speaks of lymphosarcoma in contradistinction to a lymphatic leukemia. The name is also of use as a means of avoiding a more lengthy circumlocution; but that the condition differs materially from acute leukemia is far from clear. Askanazy's theory that most, if not all, cases of chloroma are of the myelogenous type is very interesting and should be checked carefully. As already mentioned, his reasons for this assumption appear to be logical. Careful Giemsa preparations and oxydase reactions performed in various ways will help materially in this process. In one of his papers, quoted by Rowe and Hirschboeck, Askanazy states that he can produce a green reaction with ordinary pus cells, when treated with ammonia and liquor formaldehydi. He cannot secure this reaction in sections of lymph nodes or other lymphoid tissue. It is clear that this experiment has influenced him in his decision as to the myelogenous character of chloroma, as well as the other points he advances in its favor. According to his experience, the oxydase reaction alone will not solve the problem, for he failed to obtain it in his case,[1] although controls carried out on leukocytes were positive. It may be that it would be well to perform the test, as we have done, by two or more technics, as it appears to be somewhat capricious.

THE SCHICK TEST PERFORMED ON MORE THAN 150,000 CHILDREN IN PUBLIC AND PAROCHIAL SCHOOLS IN NEW YORK (MANHATTAN AND THE BRONX) *

ABRAHAM ZINGHER, M.D., Dr.P.H.
Assistant Director, Research Laboratory, Department of Health; Assistant Professor of Hygiene, New York University and Bellevue Hospital Medical College
NEW YORK

Performance of the Schick test and active immunization with toxin-antitoxin were started on a large scale in the public schools of New York during the spring of 1921. Since then the work has been continued under the general direction of Dr. Park, and nearly all the children in public and parochial schools in Manhattan and the Bronx have been tested by myself and my group of assistants. In Brooklyn and Queens the work is being carried out by Dr. Schroder and her associates. The following report represents the tabulated summary of the Schick test on more than 150,000 schoolchildren in Manhattan and the Bronx.

A. THE SCHICK TEST AND CONTROL TEST: DILUTIONS FOR THE TEST

The Schick test was made on the right forearm of each child and the control test with heated toxin on the left forearm. The reactions were read from the third to the seventh day after the test, the day of reading depending on how the work could be arranged in the schools.

We consider the proper dilution of the toxin one of the most important elements in the accuracy of the test. When large numbers of children are to be tested, the use of unheated bulk toxin for the Schick test and of heated bulk toxin for the control is recommended[1] as the most accurate and economical method for carrying on the work. It is practically the only way to prepare a large amount of a *uniform* toxin dilution and to be certain of the accuracy of the results as regards one of the essential elements in the test. From an economical point of view this method is most important as we can apply the Schick test in this way to more than 3,000 children, and the expense for the material used will amount to less than one dollar. If proper precautions are taken in making these dilutions as recommended in a

---

* Received for publication, March 8, 1923.

* Read before the Academy of Medicine, Toledo, Ohio, Jan. 15, 1923.

previous publication,[1] there will be no danger that dilutions that are too toxic will be prepared. Certainly, health officers, school physicians and general practitioners that have to test large numbers of children should be able to make the proper dilutions without the fear of any unnecessary risks.

B. SUSCEPTIBILITY TO DIPHTHERIA BY AGE PERIODS

In Table 1 and in the succeeding tables the percentages reported are significant in that they are based upon large numbers of tested individuals. Statistics regarding susceptibility and immunity to diphtheria and conclusions to which they lead should be founded on tests that are accurately carried out on many individuals. Conclusions based on a small number of tests are frequently liable to be misleading.

TABLE 1—*The Schick Test in the Public and Parochial Schools of New York (Manhattan and the Bronx)*

Age, Years	Total No. of Children Tested	Schick Positive Reactions	Schick Negative Reactions	Percentage of Schick Positive Reactions
5- 6	4,809	2.902	1,907	**60.3**
6- 7	13,754	6,944	6,810	**50.4**
7- 8	16,180	7,042	9,138	**43.5**
8- 9	17,126	6,278	10,848	**36.6**
9-10	18,065	5,825	12,240	**32.2**
10-11	18,057	5,308	12,749	**29.3**
11-12	17,994	5,075	12,919	**28.2**
12-13	16,258	4,327	11,931	**23.6**
13-14	14,138	3,271	10,867	**23.1**
14-15	9,650	1,906	7,744	**19.7**
15-16	4,861	869	3,992	**17.8**
16-17	369	68	301	**18.4**
Total	151,261	49,815	101,446	**32.9**

Table 1 gives a summary of the Schick tests carried out in the public and parochial schools in Manhattan and the Bronx. It shows the susceptibility by age periods of more than 150,000 children in a mixed population, as represented in the schools of New York. It is important to note that more than 60 per cent. of the children gave a positive Schick reaction upon entering school.

Table 2 shows the susceptibility to diphtheria of a large group of children between 6 and 12 months and between 1 and 14 years of age. In Group A are the children that were tested at the baby health stations. They represent a poorer class of the population. It is interesting to note that even in this group of the population there is a very high percentage of positive Schick reactions in children under 1 year, especially from 8 to 12 months of age. The susceptibility continues very high up to

---

[1] Zingher, Abraham: The Schick Test: Standardization of Diphtheria Toxin for the Test and of Heated Diphtheria Toxin for the Control; Methods of Diluting the Toxin, J. A. M. A. **78**:490-493 (Feb. 18) 1922.

3 years of age. It is probable that even in the poorer classes of the population the very young children are kept fairly well separated, and exposure to repeated infection is thus to a certain extent avoided. The percentage of positive reactions diminishes very rapidly after the age of 7 years.

TABLE 2.—*Group A: The Schick Test in Baby Health Stations and Play Grounds (Manhattan and the Bronx)*

Age	Total No. of Children Tested	Schick Positive Reactions	Schick Negative Reactions	Percentage of Schick Positive Reactions
6- 7 months	53	30	23	56.6
7- 8 months	41	26	15	63.4
8- 9 months	62	52	10	83.8
9-10 months	58	54	4	93.1
10-11 months	61	53	8	87.0
11-12 months	34	31	3	91.1
1- 3 years	1,727	1,433	289	83.2
4- 6 years	1,328	779	549	58.6
7-10 years	903	330	573	36.5
11-14 years	235	53	182	22.5
Total	4 502	2,846	1,656	63.2

Group B: The Schick Test in Public School Children of Kindergarten and 1A Classes

5- 6 years	327	253	64	77.15
6- 7 years	933	632	301	67.73
Total	1,260	885	365	70.25

TABLE 3.—*Results of Schick Test at Public School 52 (Manhattan)*

Age	Total No. of Children Tested	Schick Positive Reactions	Schick Negative Reactions	Percentage of Schick Positive Reactions
5- 6 years	19	16	3	84.21
6- 7 years	69	57	12	82.61
7- 8 years	114	83	31	72.81
8- 9 years	91	69	22	76.26
9-10 years	83	59	24	71.09
10-11 years	60	35	25	58.33
11-12 years	64	44	20	68.75
12-13 years	46	31	15	67.39
13-14 years	42	22	20	52.38
14-15 years	18	11	7	61.11
15-16 years	10	5	5	50.00
Total	616	432	184	70.13

In Group B the table gives by contrast the results in a series of twelve schools in which more than 77 per cent. of the children between 5 and 6 years of age had shown a positive reaction. These schools are located in the less congested sections of the city and attended by children of the more well-to-do. In this group are included a few schools in which from 85 to 90 per cent. of the children in the kindergarten and 1 A classes gave a positive Schick reaction. Table 3 gives the findings in one of these schools.

These figures emphasize the high proportion of susceptible children on admission to school and should be remembered in connection with the practical work of immunizing them against diphtheria. When too many difficulties are in the way of giving the preliminary Schick test to these young children the test could be omitted and the children simply injected with the three doses of toxin-antitoxin.

Table 4 gives the results of a more detailed study of the Schick tests on 60,100 children, which represent a part of the tests in Table 1. In this table the reactions are classified[2] as positive and positive-combined among the nonimmunes, and as negative and negative-pseudo among the immunes. The table brings out the following two interesting and important facts:

1. A considerable number of children of school age show negative-pseudo reactions. These reactions should be identified with accuracy by means of the control test.[3] The mistake will thus be avoided of interpreting them as positive Schick reactions with the resulting error of giving the children unnecessarily the injections of toxin-antitoxin. It is in this very group that the toxin-antitoxin produces the most marked local and constitutional symptoms.

2. The negative-pseudo reactions were more than two and one-half times as frequent among the immunes as the positive-combined reactions among the nonimmunes. This is additional evidence that exposure to infection with the diphtheria bacillus is an important factor in the development of the so-called "natural" antitoxic immunity. Such exposure produces not only an antitoxic immunity, but also seems to sensitize many individuals to the protein substance of the diphtheria bacillus. This sensitization appears in the form of negative-pseudo reactions in the Schick test and control test.

Table 5 gives in the last three percentage columns a comparison in age susceptibility between the children in three different groups of schools. Group I represents twelve schools in which the positive Schick reactions varied from 67 to 40 per cent.; Group II, ten schools with positive reactions from 40 to 30 per cent., and Group III, twenty-two schools with positive reactions from 30 to 13 per cent. The differences in these three groups show that the contrast in susceptibility is less definite in early school life than in later school life. The "natural" immunity to diphtheria among the children in the crowded and poorer districts increases more rapidly with advancing school years than among those of the more well-to-do.

---

[2] Zingher, Abraham: Diphtheria Prevention Work in the Public Schools of New York City, J. A. M. A. **77**:835-841 (Sept. 10) 1922.

[3] Zingher, Abraham: Methods of Using Diphtheria Toxin in the Schick Test and of Controlling the Reaction, Am. J. Dis. Child. **11**:269 (April) 1916.

TABLE 4.—*The Schick Test in the Public Schools of New York (Manhattan and the Bronx): Susceptibility to Diphtheria by Ages*

Age, Years	Total Tested	Nonimmune			Immune			Percentage of Nonimmune			Percentage of Immune		
		Schick Positive Reactions	Positive-Combined Reactions	Total Schick Positive Reactions	Schick Negative Reactions	Negative-Pseudo Reactions	Total Schick Negative Reactions	Of Total Tested	Percentage of Positive-Combined Reactions		Of Total Tested	Percentage of Negative-Pseudo Reactions	
									Of Total Tested	Of Total Schick Positive		Of Total Tested	Of Total Schick Negative
4- 5	30	21	0	21	8	1	9	70.0	0.0	0.0	30.0	3.0	11.0
5- 6	1,575	975	21	996	508	71	579	63.2	1.3	2.0	36.7	4.0	12.0
6- 7	5,377	2,586	61	2,647	2,393	337	2,730	49.2	1.0	2.0	50.8	6.0	12.0
7- 8	6,130	2,525	112	2,637	8,010	483	3,494	43.0	2.0	4.0	57.0	8.0	14.0
8- 9	6,539	2,176	187	2,363	3,484	692	4,176	36.1	2.8	8.0	63.9	10.0	16.0
9-10	7,071	2,029	125	2,224	3,802	1,045	4,847	31.4	2.7	9.0	68.6	14.0	21.0
10-11	7,205	1,867	197	2,064	3,997	1,164	5,141	28.6	2.7	9.0	71.4	16.0	22.0
11-12	7,344	1,901	222	2,123	4,063	1,158	5,221	28.9	3.0	10.0	71.1	16.0	22.0
12-13	6,405	1,608	212	1,820	3,748	837	4,585	28.4	3.0	11.0	71.6	13.0	18.0
13-14	6,252	1,188	227	1,415	3,466	1,371	4,837	22.6	3.0	16.0	77.4	22.0	28.0
14-15	4,147	669	123	792	2,520	832	3,352	19.1	3.0	15.0	80.9	20.0	25.0
15-16	1,760	270	50	320	1,068	372	1,440	18.1	3.0	16.0	81.9	21.0	26.0
16-17	247	38	11	49	154	44	198	19.8	4.0	23.0	80.1	18.0	22.0
17-18	18	2	0	2	14	2	16	11.1	0.0	0.0	88.9	11.0	12.0
Total	60,100	17,855	1,618	19,473	32,235	8,409	40,624	32.6	2.7	8.3	67.4	14.0	20.7

TABLE 5.—*Susceptibility to Diphtheria by Ages in the Public Schools of New York (Manhattan and the Bronx) Classified by School Group*

Age, Years	Group I		Group II		Group III		Percentage of Schick Positive Reactions		
	Twelve Schools Schick Positive 67-40 per Cent.		Ten Schools Schick Positive 40-30 per Cent.		Twenty-two Schools Schick Positive 30-13 per Cent.				
	Total Tested	Schick Positive Reactions	Total Tested	Schick Negative Reactions	Total Tested	Schick Positive Reactions	Group I	Group II	Group III
4- 5.........	6	6	9	6	15	9	100.0	66.6	60.0
5- 6.........	376	283	257	153	723	337	75.2	59.5	46.6
6- 7.........	1,142	775	992	501	2,276	840	67.8	50.5	32.5
7- 8.........	1,315	782	1,246	531	2,709	878	51.1	42.6	32.4
8- 9.........	1,390	774	1,331	500	3,090	788	55.6	37.6	25.5
9-10.........	1,382	669	1,473	521	3,507	801	48.4	35.5	22.8
10-11.........	1,276	563	1,340	461	3,851	816	44.1	34.4	21.1
11-12.........	1,348	633	1,380	485	3,905	782	46.9	35.1	20.0
12-13.........	1,164	471	1,267	377	3,700	744	40.4	29.7	19.8
13-14.........	966	354	1,067	284	3,415	571	36.3	26.6	16.6
14-15.........	665	201	730	193	2,285	266	30.2	26.4	11.6
15-16.........	312	87	295	74	947	113	27.9	25.1	11.9
16-17.........	73	27	35	5	136	17	37.0	14.3	12.5
Total......	11,415	5,625	11,422	4,091	30,619	6,962	49.2	35.8	22.7

C. SUSCEPTIBILITY TO DIPHTHERIA INFLUENCED BY SOCIAL AND RACIAL FACTORS

In the following four tables the schools are arranged in the order in which the children showed positive Schick reactions, the schools with the highest percentage appearing first.

Tables 6 and 7 give the results obtained in a series of individual public schools in the borough of Manhattan. Table 6 shows schools with positive Schick reactions varying from 70 to 30 per cent. Many of these schools are located in better sections of the city and attended by children of a more well-to-do class than those enumerated in Table 7 in which the schools show positive reactions varying from 30 to 14 per cent. It is interesting to note that of sixty-eight schools in the borough of Manhattan there are twenty-seven schools in the group of higher percentages as compared with the forty-one schools in the group of lower percentages.

TABLE 6.—*The Schick Test in the Public Schools of Manhattan, New York*

Public School	Location	Nonimmunes			Immunes			Total Tested	Per Cent. Schick Positive Reactions
		Schick Positive Reactions	Schick Positive-Combined Reactions	Total Schick Positive Reactions	Schick Negative Reactions	Schick Negative-Pseudo Reactions	Total Schick Negative Reactions		
52	Broadway and Academy St..	395	37	432	126	58	184	616	**70.13**
9	82d St. and West End Ave....	161	13	174	91	34	125	299	**58.53**
6	Madison Ave. and 85th St....	180	15	195	113	29	142	337	**57.86**
165	108th St. and Amsterdam Ave.	295	10	305	158	70	228	533	**57.22**
166	89th St. near Columbus Ave..	157	8	165	92	41	133	298	**55.35**
115	177th St. and St. Nicholas Ave.	327	29	356	188	132	320	676	**52.66**
93	Amsterdam Ave. and 93d St..	287	22	309	185	105	290	599	**51.59**
10*	St. Nicholas Ave. and 117th St.	329	17	346	244	95	339	685	**50.51**
94	Amsterdam Ave. and 68th St.	316	20	336	369	77	446	782	**42.96**
179	102d St. and Amsterdam Ave.	227	10	237	317	22	339	576	**41.14**
56	18th St. and 9th Ave.........	202	23	225	271	51	322	547	**41.13**
87	77th St. and Amsterdam Ave.	156	9	165	213	29	242	407	**40.54**
50	20th St. and 3d Ave..........	145	16	161	249	19	268	429	**37.52**
63	4th St. and 1st Ave..........	383	44	427	672	88	760	1,187	**35.96**
51	44th St. and 10th Ave........	289	23	312	525	53	578	890	**35.05**
170*	111th St. and Lenox Ave.....	143	10	153	236	52	288	441	**34.69**
190	82d St. and 2d Ave...........	196	5	201	362	25	387	588	**34.18**
18	51st St. and Lexington Ave..	125	2	127	226	20	246	373	**34.03**
141	58th St. and 9th Ave.........	183	9	192	328	53	381	573	**33.51**
28	40th St. and 8th Ave.........	200	9	209	374	51	425	634	**32.96**
73	46th St. and 3d Ave..........	157	0	157	300	29	329	486	**32.29**
36	9th St. and Avenue C.........	208	7	215	422	32	454	669	**32.15**
86	Lexington Ave. and 96th St..	320	25	345	539	200	739	1,084	**31.83**
10†	St. Nicholas Ave. and 117th St.	155	13	168	253	108	361	529	**31.76**
71	7th St. and Avenue B.........	168	46	214	367	94	461	675	**31.70**
13	E. Houston and Essex Sts...	310	16	326	671	32	703	1.029	**31.63**
65	Eldridge and Hester Sts......	423	5	428	885	39	934	1,352	**31.66**

* Primary. † Boys.

Table 8 presents the results of tests in the public schools in the borough of the Bronx. In twenty-nine of these public schools the children gave positive Schick reactions varying from 63 to 32 per cent. and in only four schools from 28 to 17 per cent.

A similar contrast in the susceptibility of school children is found by comparing the parochial schools of Manhattan with those in the Bronx, as seen in Table 9.

These tables illustrate the well-known fact that in the more recently developed borough of the Bronx there are fewer sections associated with congestion and crowding of the population than in the older borough of Manhattan.

TABLE 7.—*The Schick Test in the Public Schools of Manhattan, New York*

Public School	Location	Nonimmunes			Immunes			Total Tested	Per Cent. Schick Positive Reactions
		Schick Positive Reactions	Schick Positive-Combined Reactions	Total Schick Positive Reactions	Schick Negative Reactions	Schick Negative-Pseudo Reactions	Total Schick Negative Reactions		
122	9th St. and 1st Ave...........	333	10	343	765	39	804	1,147	**29.90**
58	52d St. and 8th Ave...........	130	9	139	320	9	329	468	**29.70**
76	Lexington Ave. and 68th St..	135	8	143	283	61	344	487	**29.36**
79	1st St. and 1st Ave...........	191	11	202	455	34	489	691	**29.23**
105	E. 4th St. and Avenue B......	108	12	120	266	32	298	418	**28.70**
135	1st Ave. and 51st St..........	206	209	235	395	192	587	822	**28.52**
32	35th St. and 9th Ave..........	167	16	183	391	74	465	648	**28.24**
170*	111th St. and Lenox Axe.....	156	19	175	310	135	445	620	**28.23**
184	116th St. and Lenox Ave.....	477	52	529	1,001	348	1,349	1,878	**28.17**
4	Rivington and Ridge Sts.....	162	27	189	446	40	486	675	**28.00**
137	Grand and Essex Sts.........	168	5	173	429	26	455	628	**27.54**
88	Rivington and Lewis Sts.....	187	18	205	504	48	552	757	**27.08**
151	1st Ave. and 91st St..........	149	25	174	373	96	469	643	**27.06**
27	41st St. and 3d Ave...........	209	23	232	499	134	633	865	**26.82**
22	Stanton and Sheriff Sts......	262	15	277	737	21	758	1,035	**26.76**
31	Monroe and Gouverneur St..	237	34	271	655	104	759	1,030	**26.31**
150	96th St. and 2d Ave...........	257	12	269	667	93	760	1,029	**26.14**
59	57th St. and 3d Ave...........	193	18	211	439	158	597	808	**26.11**
160	Rivington and Suffolk Sts...	223	15	238	646	28	674	912	**26.09**
110	Broome and Cannon Sts.....	159	13	172	424	65	489	661	**26.02**
92	Broome and Ridge Sts.......	233	13	246	636	88	724	970	**25.36**
25	5th St. and 1st Ave...........	339	16	355	885	161	1,046	1,401	**25.31**
12	Madison and Jackson Sts....	302	52	354	865	175	1,040	3,194	**25.32**
38	Broome and Clark Sts.......	120	5	125	334	35	369	494	**25.30**
91	Stanton and Forsyth Sts....	272	49	321	773	206	979	1,300	**24.69**
82	1st Ave. and 70th St..........	100	11	111	266	74	340	451	**24.61**
40	20th St. and 1st Ave..........	56	8	64	167	30	197	261	**24.52**
70	75th St. and 3d Ave...........	159	15	174	472	88	552	726	**23.97**
104	16th St. and 1st Ave..........	158	32	190	468	169	637	827	**22.97**
121	102d St. and 3d Ave...........	215	25	240	552	274	826	1,066	**22.51**
140	Norfolk and Rivington Sts...	122	4	126	410	24	434	560	**22.50**
1	Henry and Oliver Sts.........	257	28	285	930	68	998	1,283	**22.20**
35	Chrystie and Delancy Sts....	176	9	185	630	49	679	864	**21.41**
114	Oak and James Sts...........	232	23	255	915	37	952	1,207	**21.11**
147	E. B'way and Gouverneur St.	196	17	213	735	129	864	1,077	**19.78**
74	63d St. and 3d Ave............	199	29	228	739	224	963	1,191	**19.14**
109	99th St. and 2d Ave...........	221	31	252	918	196	1,114	1,366	**18.45**
21	Mott and Elizabeth Sts......	315	16	331	1,415	104	1,519	1,850	**17.88**
97	Mangin and Stanton Sts.....	107	6	113	504	61	565	6.8	**16.66**
34	Broome and Sheriff Sts......	75	4	79	364	31	395	474	**16.66**
23	Mulberry and Bayard Sts....	126	25	151	756	126	882	1,033	**14.62**

* Girls.

The racial factor may also be noted in these tables. The schools in which there is the highest percentage of positive Schick reactions are attended largely by native born children of American parents. The schools showing the lowest percentage of positive Schick reactions are those attended to a great extent by children of Italian parents. The other schools with percentages varying between these extremes are attended by children of more recently immigrated Jewish, Russian,

Table 8.—*The Schick Test in the Public Schools of the Bronx, New York*

Public School	Location	Nonimmunes			Immunes			Total Tested	Per Cent. Schick Positive Reactions
		Schick Positive Reactions	Schick Positive-Combined Reactions	Total Schick Positive Reactions	Schick Negative Reactions	Schick Negative-Pseudo Reactions	Total Schick Negative Reactions		
26	Andrews and Burnside Aves..	206	4	210	110	12	122	332	63.25
46	196th St. and Driggs Ave.....	248	13	261	122	32	154	415	62.90
33	Jerome and Walton Aves....	214	11	225	87	47	134	359	62.67
35	163d St. and Grant Ave.......	338	12	350	188	24	212	562	82.27
28	Tremont and Anthony Aves.	271	18	289	166	47	213	302	57.57
6	Tremont and Vyse Aves......	548	7	555	377	45	422	977	56.81
48	Coster and Faile Sts.........	447	11	458	374	54	428	886	51.69
44	Prospect Ave. and 176th St...	288	78	366	202	145	347	713	51.33
25	149th St. and Union Ave......	392	57	449	354	131	485	934	43.00
53	E 168th St. and Findlay Ave.	410	22	432	370	127	497	929	46.50
2	3d Ave. and 169th St..........	273	15	388	410	47	457	845	45.92
59	Bathgate Ave. and 182d St...	254	16	270	259	61	320	490	45.76
10	Eagle Ave. and 163d St.......	348	40	388	335	125	460	848	45.70
57	180th St. and Belmont Ave...	486	34	520	476	142	618	1,138	45.69
20	Fox and 167th Sts............	365	31	396	347	135	482	878	45.10
23	165th St. and Tinton Ave.....	358	12	370	392	73	465	835	44.31
39	Longwood and Kelly Sts.....	278	28	306	248	172	420	726	42.15
50	Bryant Ave. and 172d St.....	458	47	505	462	322	784	1,289	39.18
30	141st St. and Brook Ave......	241	64	305	292	214	506	811	37.61
37	145th St. and Willis Ave......	236	28	264	285	158	443	707	37.34
5	Webster Ave. and 189th St...	161	19	180	284	106	290	489	36.80
27	St Anns Ave. and 147th St...	359	65	424	412	385	797	1,221	34.70
51	158th St. and Jackson Ave...	262	25	287	387	156	543	830	34.58
32	183d St. and Beaumont Ave..	622	19	641	1,070	148	1,218	1,859	34.48
29	Cypress Ave. and 135th St....	314	54	368	427	285	712	1,080	34.07
55	St. Pauls Pl. and Wash. Ave.	416	40	456	712	230	942	1,398	32 62
9	138th St. and Brook Ave.....	257	28	285	484	120	604	889	32.06
45	189th and Hoffman Sts.......	521	20	541	1,221	133	1,354	1,895	28.55
31	Mott Ave. and 144th St.......	136	7	143	429	42	471	614	23.30
4	Fulton Ave. and 173d St......	193	55	248	462	423	885	1,133	21.60
1	Colledge Ave. and 145th St...	85	17	102	309	180	489	591	17.25

Table 9.—*The Schick Test in Parochial Schools in Manhattan and the Bronx, New York*

School and Location	Schick Positive Reactions	Schick Positive-Combined Reactions	Total Schick Positive Reactions	Schick Negative Reactions	Schick Negative-Pseudo Reactions	Total Schick Negative Reactions	Total Tested	Per Cent. Schick Positive Reactions
St. Thomas Aquinas, 1915 Daley Ave., Bronx..............................	156	2	158	109	18	127	285	54.73
St. Augustine, 167th St. and Fulton Ave., Bronx........................	143	2	145	190	14	204	349	41.50
St. Jerome, 137th St. and Alexander Ave., Bronx........................	102	2	104	139	31	170	274	39.75
Cathedral, 50th St. and Lexington Ave., Manhattan...................	90	8	98	138	54	192	290	33.79
St. Gabriel, 36th St. and 8th Ave., Manhattan........................	163	3	166	328	38	366	532	31.20
St. John the Evangelist, 50th St and 1st Ave., Manhattan...............	87	14	101	162	74	236	337	29.84
St. Monica, 80th St. and 1st Ave., Manhattan........................	91	26	117	165	113	278	395	29.60
St. Bernard (Girls), 13th St. and 9th Ave., Manhattan,..................	102	27	129	184	126	310	439	29.30
St. Stephen, 28th St. and Lexington Ave., Manhattan..................	69	6	75	169	20	189	264	28.40
Sacred Heart, 51st St. and 10th Ave., Manhattan........................	209	8	217	433	119	552	769	28.22
Resurrection, 151st St. and 8th Ave., Manhattan........................	66	3	69	155	34	189	258	26.66
Immaculate Conception, 14th St. and Avenue A, Manhattan............	83	2	85	247	46	293	378	22.49
St. Bernard (Boys), 13th St. and 9th Ave., Manhattan..................	75	12	87	224	91	315	402	21.11
St. Anthony, 62 Macdougal St., Manhattan..............................	62	0	62	240	4	244	306	20.26
St. Patrick (Girls), 233 Mott St., Manhattan..............................	176	3	179	642	48	790	969	18.50
St. Patrick (Boys), 268 Mulberry St., Manhattan........................	51	1	52	333	7	340	392	13.23

Polish, Czechoslovacian, Irish parents, etc., one or two of these nationalities frequently predominating in some of the schools. Table 9 giving the percentage of positive Schick reactions among children in parochial schools is also interesting in showing that overcrowding and repeated exposure to infection are really more important than race as factors in natural immunity to diphtheria. The three schools in the Bronx in which the children gave the highest percentage of positive Schick reactions are attended largely by children of Irish extraction. On the other hand, some of the schools in Manhattan which show a very low percentage of positive reactions, as for instance St. Bernard's, are also attended mostly by children of Irish parentage. It is significant to note that the school with the lowest percentage of positive Schick reactions, St. Patrick's, is located in the most congested section of the city, in which the population is nearly all Italian.

Table 10.—*The Schick Test in the Public School of Metuchen, N. J.; Caldwell, N. J.; Verona, N. J., and Cedar Grove, N. J.*

Age, Years	Nonimmune			Immune			Total Tested	Percentage of Schick Positive Reactions
	Schick Positive Reactions	Positive-Combined Reactions	Total Schick Positive Reactions	Schick Negative Reactions	Negative Pseudo Reactions	Total Schick Negative Reactions		
5- 6	62	0	62	7	0	7	69	89.8
6- 7	73	0	73	11	1	12	85	85.8
7- 8	82	0	82	13	1	14	96	85 4
8- 9	93	0	93	22	2	24	117	79.5
9-10	75	0	75	24	2	26	101	74.2
10-11	61	0	61	21	9	30	91	67.0
11-12	74	1	75	19	4	23	98	76.5
12-13	62	2	64	20	4	24	88	72.7
13-14	64	2	66	17	7	24	90	73.3
14-15	22	1	23	11	2	13	36	63.9
15-16	41	2	43	10	4	14	57	75.4
16-17	39	1	40	11	5	16	56	71.4
Total	748	9	757	186	41	227	984	76.9

The results stated in these tables correspond closely to those that were reported in a previous communication [2] in a series of forty-four schools in Manhattan and the Bronx.

Table 10 shows the very high percentage of positive Schick reactions in public schools located in small suburban towns, attended to a large extent by children of a more well-to-do class. Many of those that gave negative reactions were children of foreign parents recently settled in town.

Table 11 gives the results of the Schick test in four public schools located in Union Hill, N. J. The schoolchildren can be divided fairly evenly into two groups, those of American born and those of foreign born parents. Among the latter we found a much higher proportion of negative Schick reactors.

D. SUSCEPTIBILITY TO DIPHTHERIA BY SEX

In our previous work with the Schick test, covering a period of more than nine years, we have generally found a larger number of positive reactions among females than among males.

Table 12 shows a definitely higher percentage of positive Schick reactions among girls than among boys. Among the girls there is also a higher proportion of negative-pseudo and positive-combined reactions.

TABLE 11.—*The Schick Test in the Public Schools of Union Hill, N. J.*

Age, Years	Schick Positive Reactions	Schick Positive-Combined Reactions	Total Schick Positive Reactions	Schick Negative Reactions	Schick Negative-Pseudo Reactions	Total Schick Negative Reactions	Total Tested	Percentage of Schick Positive Reactions
5– 6	46	0	46	22	1	23	69	**66.66**
6– 7	49	1	50	42	3	45	95	**52.63**
7– 8	59	4	63	60	9	69	132	**47.72**
8– 9	55	5	60	55	14	69	129	**46.51**
9–10	44	5	49	62	22	84	133	**36.84**
10–11	43	6	49	59	30	89	138	**35.50**
11–12	40	5	45	63	31	94	139	**32.37**
12–13	35	7	42	73	30	103	145	**29.00**
13–14	56	9	65	77	53	130	195	**33.33**
14–15	46	10	56	46	30	76	132	**42.42**
15–16	14	7	21	24	11	35	56	**37.50**
16–17	6	0	6	6	2	8	14	**42.85**
Total	493	59	552	589	236	825	1,377	**40.00**

TABLE 12.—*Comparison of Susceptibility to Diphtheria Between Boys and Girls in New York Public Schools (Public Schools 188, 39, 83, 159, Manhattan)*

Age, Years	Boys		Girls		Percentage of Schick Positive Reactions		Percentage of Negative-Pseudo Reactions of Immunes		Percentage of Positive-Combined Reactions of Nonimmunes	
	Total	Schick Positive Reactions	Total	Schick Positive Reactions	Boys	Girls	Boys	Girls	Boys	Girls
5– 6	74	35	60	27	**46.0**	**45.0**	**17.5**	**21.2**	**0**	**0**
6– 7	195	74	207	84	**37.8**	**40.6**	**8.2**	**24.4**	**4.1**	**1.0**
7– 8	248	83	244	93	**33.4**	**33.1**	**11.5**	**23.2**	**3.6**	**5.3**
8– 9	277	76	219	68	**27.4**	**31.5**	**15.0**	**22.2**	**5.2**	**11.8**
9–10	393	86	281	82	**21.9**	**39.2**	**21.5**	**30.6**	**7.0**	**15.8**
10–11	675	147	264	62	**21.8**	**23.4**	**24.2**	**38.1**	**12.7**	**16.1**
11–12	782	153	299	72	**19.5**	**24.1**	**26.8**	**31.7**	**18.3**	**15.3**
12–13	783	116	479	99	**14.8**	**20.7**	**26.5**	**36.0**	**14.6**	**21.2**
13–14	740	91	497	100	**12.3**	**20.1**	**26.6**	**35.7**	**19.7**	**23.0**
14–15	500	65	361	67	**13.0**	**21.3**	**27.6**	**29.5**	**23.1**	**19.4**
15–16	224	17	155	21	**7.5**	**13.4**	**18.3**	**36.5**	**0.0**	**23.3**
16–17	31	2	21	3	**6.4**	**14.3**	**27.6**	**33.3**	**0.0**	**33.3**
Total	4,922	945	3,087	778	**19.2**	**25.3**	**23.7**	**32.3**	**11.9**	**14.2**

In Table 13 are given the results of the Schick test on more than 6,000 adult inmates of an insane asylum. The table brings out the fact that even among those who are far advanced in years there is a definite though small percentage of positive Schick reactors. It shows that repeated exposure even over a long period of years does not produce an antitoxic immunity in certain individuals. These figures help to explain why it is difficult to develop an active immunity in a small percentage of individuals even with several series of toxin-antitoxin injections. There is a partial or nearly total inability of the tissues in some people to respond to the immunizing effects of certain antigens. This resistance is probably hereditary in character.

The table also shows a higher percentage of positive Schick reactions among adult females than among males.

E. "NATURAL" IMMUNITY TO DIPHTHERIA

In the preceding tables we have seen some of the important factors active in the development of spontaneous immunity to an endemic infectious disease. These factors consist of crowding and repeated exposure to infections with the diphtheria bacillus. In cities this organism is constantly present. From 2 to 3 per cent. of the inhabitants are carriers of virulent diphtheria bacilli. The high percentage of positive Schick reactions among the children of the more well-to-do and the low percentage among those of the poorer classes show the importance of overcrowding in the development of immunity. In the smaller communities and especially in rural sections where the people live more or less segregated, the percentage of positive Schick reactions is very high. In rural schools we have seen from 85 to 90 per cent. of positive Schick reactions. This is true not only for children but also for adults. In various city hospitals we have tested groups of nurses, many of whom had only recently come to the city from smaller communities, and have found that among them from 50 to 75 per cent. gave a positive reaction to the Schick test. Similar observations were reported

TABLE 13.—*The Schick Reaction in Advanced Age Groups (Manhattan State Hospital)*

Age, Years	Schick Positive Reactions	Schick Positive-Combined Reactions	Total Schick Positive Reactions	Schick Negative Reactions	Schick Negative-Pseudo Reactions	Total Schick Negative Reactions	Total Tested	Percentage of Schick Positive Reactions
Males—								
10-20	12	1	13	57	18	75	88	**14.7**
20-30	47	8	55	551	99	650	705	**7.8**
30-40	45	11	56	580	110	690	746	**7.5**
40-50	28	2	30	418	69	487	517	**5.8**
50-60	21	1	22	292	20	312	334	**6.5**
60-70	5	0	5	142	4	146	151	**3.3**
Over 70	2	0	2	59	1	60	62	**3.2**
Total	160	23	183	2,099	321	2,420	2,603	**7.0**
Females—								
10-20	9	2	11	60	9	69	80	**13.7**
20-30	76	15	91	376	81	457	548	**16.6**
30-40	89	13	102	514	126	640	742	**13.7**
40-50	58	12	70	546	87	633	703	**9.9**
50-60	34	3	37	466	83	549	586	**6.3**
60-70	30	1	31	446	34	480	511	**6.6**
Over 70	8	0	8	107	4	111	119	**6.7**
Total	304	46	350	2,515	424	2,939	3,289	**10.0**

to me in a personal communication by Dr. Charles W. Kidder, District Health Officer of Woodstock, Vermont. He gave the Schick test to 2,030 children and found in rural towns, with a very high percentage of native born children, as high as 96 per cent. of positive reactors. In the larger villages on the railroad and in villages containing a large percentage of foreign population, he obtained correspondingly fewer positive Schick reactors, the lowest percentage being 60. Of eighty-seven teachers between the ages of 20 and 60 years, 82 per cent. gave a positive reaction.

Table 14 is an interesting study of the effect of close contact in an institution. It gives the results of the Schick test in an institution in which most of the children came from New York City. Under "Institution" children are included those that have been at the institution three months or longer; under "Preventorium" children those who have been there less than three months.

TABLE 14.—*The Schick Test at St. Agatha's Home, Nanuet, N. Y.*

Age, Years	Institution Children						Preventorium Children (Less Than Three Months in the Institution)			
	Total Tested	Schick Negative Reactions	Negative-Pseudo Reactions	Total Immune	Schick Positive Reactions	Percentage of Schick Positive Reactions	Total Tested	Schick Negative Reactions	Schick Positive Reactions	Percentage of Schick Positive Reactions
2– 3.........	8	4	0	4	4	50.0	0	0	0	0
3– 4.........	13	8	0	8	5	38.5	0	0	0	0
4– 5.........	21	16	0	16	5	23.8	6	2	4	66.6
5– 6.........	22	15	1	16	6	27.3	6	4	2	33.3
6– 7.........	53	42	2	44	9	17.0	7	4	3	43.0
7– 8.........	36	25	6	31	5	13.9	16	9	7	43.7
8– 9.........	44	35	7	42	2	4.6	9	6	2	33.3
9–10.........	54	44	8	52	2	3.6	11	10	1	9.0
10–11.........	63	59	3	62	1	1.6	9	6	3	33.3
11–12.........	59	46	10	56	3	5.0	8	6	2	25.0
12–13.........	67	51	13	64	3	4.5	2	1	1	50.0
13–14.........	50	37	9	46	4	8.0	3	3	0	0.0
14–15.........	38	30	6	36	2	5.3	1	1	0	0.0
15–16.........	15	11	4	15	0	0.0	0	0	0	0.0
Total......	543	423	69	492	51	9.4	78	52	26	33.3
Total*.....	520	...	...	492	28†	5.4	...	...	...	33.3

* Excluding twenty-three children giving a positive reaction who had been less than three months in the institution.

† Of the twenty-eight children giving a positive reaction, twenty had been in the institution between three months and two years.

Among the "Preventorium" children, twenty-six of a total of seventy-eight, or 33.3 per cent., gave a positive Schick reaction. This is in striking contrast to the "Institution" children of whom only twenty-eight of a total of 520, or 5.4 per cent., gave positive reactions. Even among the twenty-eight positively reacting "Institution" children, fully twenty had been in the institution only from three months to two years. Frequent contact in the institution explains these results.

Dudley[4] has recently reported the results of the Schick test in an institution in which diphtheria had been prevalent and had resulted in a large number of carriers. This study furnishes additional evidence that exposure to infection with the diphtheria bacillus is an important factor in the development of contact or so-called "natural" immunity.

Without going too far astray one could probably generalize from "natural" immunity against diphtheria to "natural" immunity against some of the other infectious diseases. Such immunity is seen in a large group of city born and city bred people who have never had these infections. Russell has drawn our attention to the fact that, during the recent war, epidemics of infectious diseases swept, as a rule, through camps in which the soldiers were recruited from the smaller towns and villages and from rural sections of the states. Many city children are often found to be relatively immune to some of these infectious diseases although they give no history of having had the infections. Herrman's[5] observations on immunity to measles also bear on this point. It has, of course, been often assumed that repeated exposure to infectious diseases, or to the carriers of their viruses or bacteria, is the chief factor in "natural" immunity; but so far it is only in diphtheria that we have been able to demonstrate this with any degree of scientific accuracy.

SUMMARY AND CONCLUSIONS

1. More than 150,000 children have been given the Schick test during the last two years in the public and parochial schools of the boroughs of Manhattan and the Bronx.

2. A high percentage of positive Schick reactions is found among the children in the entering classes in the kindergarten and 1 A grades. This varies in different schools from 60 to 85 per cent. The toxin-antitoxin injections could, therefore, be given to these young children without the preliminary Schick test.

3. The schools located in the less congested sections of the city and attended by children of the more well-to-do show, as a rule, from 100 to 200 per cent. more Schick positive reactors than those located in the crowded parts and attended by children of the poorer classes.

4. Repeated exposure to infection with the diphtheria bacillus is probably the most important factor in the development of "natural" immunity to this disease. Racial and hereditary family factors, although less important, also play a rôle.

---

[4] Dudley, S. F.: The Relation of Natural Diphtheria Antitoxin in the Blood of Man to Previous Infection with Diphtheria Bacilli, Brit. J. Exper. Path. **3**:204-210 (Aug.) 1922.

[5] Herrman, Charles: Immunization Against Measles, Arch. Pediat. **39**: 607-610 (Sept.) 1922.

5. Girls show a somewhat larger percentage of positive Schick reactions than boys. They also show more negative-pseudo and positive-combined reactions. This holds true also for adults.

6. The high percentage of positive Schick reactors among young children of preschool age may, under certain conditions, render it advisable to simplify the procedure of immunization by omitting the preliminary Schick test. The children are simply injected with three doses of toxin-antitoxin. Under these circumstances, however, the children should not be pronounced immune to diphtheria until a supplementary Schick test, performed six months later, proves negative.

7. Diphtheria is the foremost fatal disease in children from 3 to 5 years of age, and ranks third among the fatal diseases of children from 1 to 3 years of age. Only diarrhea and pneumonia precede diphtheria in the mortality tables. The dangerous laryngeal form occurs in the young children. It is for these reasons that physicians should urge parents to take advantage of these newer methods to protect their young children against diphtheria. In fact, active immunization against diphtheria should become as much of a routine for all children between 6 months and 6 years as vaccination is against smallpox today.

THE WATER CONTENT OF INFANTS' BLOOD DURING PERIODS OF RAPID INCREASE IN WEIGHT *

HARRY BAKWIN, M.D.

NEW YORK

These studies were undertaken in order to determine whether or not there is an increase in the water content of the blood during the rapid gains in weight which not infrequently occur in healthy, artificially fed infants. Freund [1] has shown that these large weight increases are due to water retention. He studied the nitrogen and chlorid balance in a series of artificially fed infants and found that during the days of rapid gain the nitrogen retention was sufficient to account for only a small part of the increase in weight. That the major part was due to water retention was shown by the marked diminution in the elimination of chlorid and alkali salts.

In these studies the refractometric method was used to determine variations in the blood water. The technic employed was similar to that described in previous papers.[2] The serum proteins were calculated from the refractive index of serum according to the formula of Reiss.[3]

Five babies were used in this study. The babies chosen were healthy in the sense that they were not suffering from acute illnesses. Some of them were slightly underweight. In most instances, the weight gains were induced by increasing the carbohydrate content of the feeding. Edema never occurred. The weighings were made by a nurse, specially assigned to the care of the babies. Blood determinations were made at frequent intervals before and after the weight gains.

REPORT OF CASES

Case 1 (Fig. 1).—S. W., a healthy boy, aged 3 months, was first observed, Nov. 3, 1920, when he weighed 4,100 gm. His feedings consisted of 450 c.c. of whole milk, 45 gm. of lactose and 360 c.c. of barley water.

November 8, the lactose in the feeding was increased to 105 gm. A sharp rise in weight followed, the baby gaining 450 gm. during the next seven days,

---

* Received for publication, April 16, 1923.

* From the Pediatric Division of the New York Nursery and Child's Hospital, and the Department of Pediatrics, Cornell University Medical College.

[1] Freund, W.: Wasser und Salze in ihren Beziehungen zu den Körpergewichtsschwankungen der Saüglinge, Jahrb. f. Kinderh. **59**:421, 1904.

[2] Bakwin, Harry: Dehydration in the New-Born, Am. J. Dis. Child. **24**:497 (Dec.) 1922.

[3] Reiss, E.: Die refraktometrische Blutuntersuchungen und ihre Ergebnisse für die Physiologie und Pathologie des Menschen, Ergebn. d. inn. Med. u. Kinderh. **10**:531, 1913.

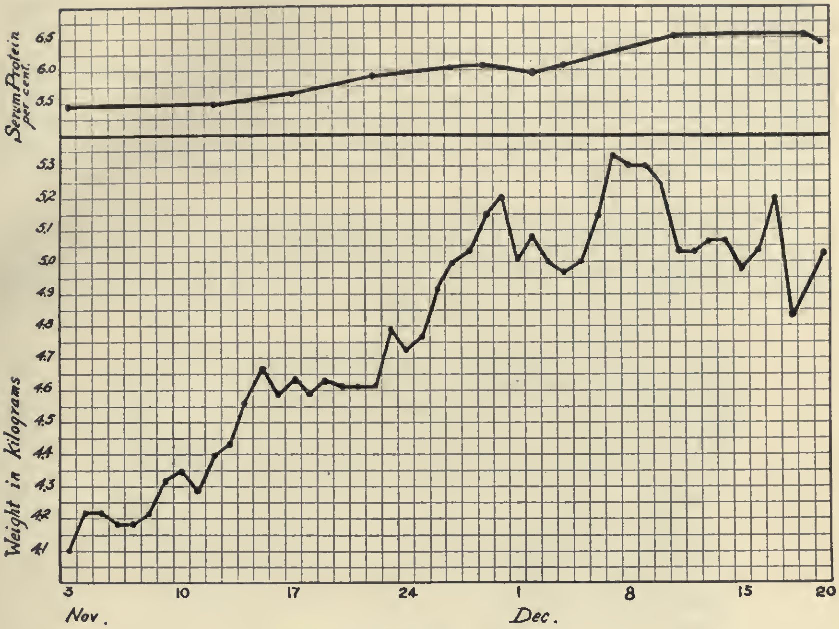


Chart 1.—Findings in Case 1.

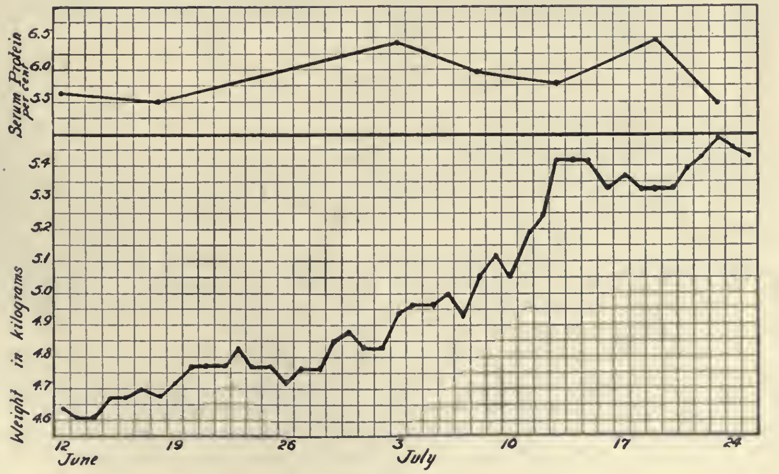


Chart 2.—Findings in Case 2.

an average daily gain of 65 gm. The weight remained stationary after this, and, November 19, the lactose was further increased to 150 gm., the amount of milk and water in the formula remaining unchanged. There was a slight gain in weight.

November 24, 180 gm. of maltose were substituted for the lactose in the feeding. This was followed by a sharp rise in weight so that the baby gained 470 gm. between the twenty-fourth and the thirtieth of November, an average daily gain of 79 gm. During this period the stools were frequent and slightly watery. December 1, the maltose was omitted from the feeding. The weight remained stationary, and the stools diminished in number and improved in consistency.

December 4, 180 gm. of maltose were again added to the feeding. Again a sharp rise in weight occurred, the baby gaining 360 gm. in three days. The maltose was again omitted from the feeding. The baby lost weight sharply. December 12, 30 gm. of maltose were added to the feeding, and, December 16 this was increased to 45 gm. The second increase in the diet was followed by a sharp rise and then by a fall in weight.

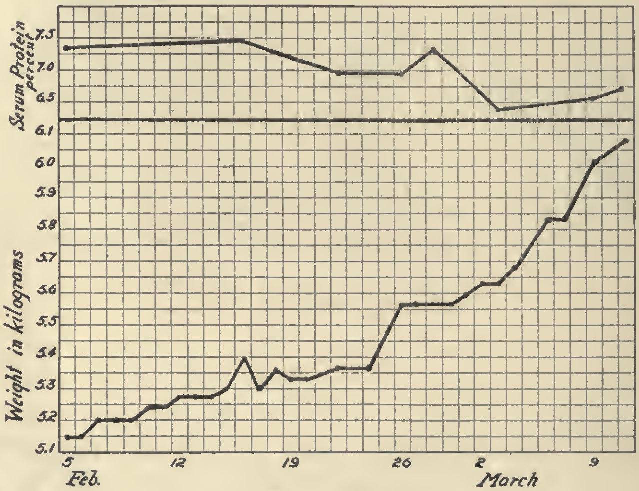


Chart 3.—Findings in Case 3.

Despite the marked variations in the weight, the serum proteins were little affected. They rose slowly and regularly from 5.45, November 3, to 6.55 per cent., December 21.

Case 2 (Fig. 2).—H. T., a healthy boy, aged 2½ months, was first observed, June 13, 1920, when he weighed 4,640 gm. He was receiving a feeding consisting of 450 c.c. of whole milk, 60 gm. of dextrimaltose and 450 c.c. of barley water, on which he gained slowly.

June 6, the dextrimaltose in the feeding was increased to 75 gm. and, June 9, to 90 gm. Following the second increase, there was a sharp rise in the weight, the baby gaining 370 gm. in three days. Coincident with the rapid gain in weight, there was a slight fall in the serum proteins from 5.9 per cent., July 8, when the weight was 5,050 gm. to 5.6, July 13, when the weight was 5,420 gm. The fall in serum protein concentration was only slightly greater than could be accounted for by errors inherent in the method for the collection and examination of the blood specimens.

Case 3 (Fig. 3).—A. G., a healthy boy, aged 3 months, was admitted, Jan. 24, 1920, when he weighed 5,000 gm. He had been under treatment for congenital syphilis in the outpatient department since birth, but he showed no active lesions during his stay in the hospital. The blood Wassermann reaction was negative.

The infant was given a feeding consisting of 660 c.c. of whole milk, 60 gm. of lactose, and 240 c.c. of barley water, on which he gained slowly. Feb. 25, 1920, the lactose in the feeding was increased to 75 gm. Between February 24 and February 26, the baby gained 200 gm. During the marked increase in weight the serum protein precentage remained unchanged, indicating that the plasma water was not increased. On March 4, the lactose in the feeding was further increased to 105 gm. During the following six days, the baby gained 380 gm., an average daily gain of 63 gm. Here again there was no fall in the serum protein concentration during or after the periods of rapid weight gain.

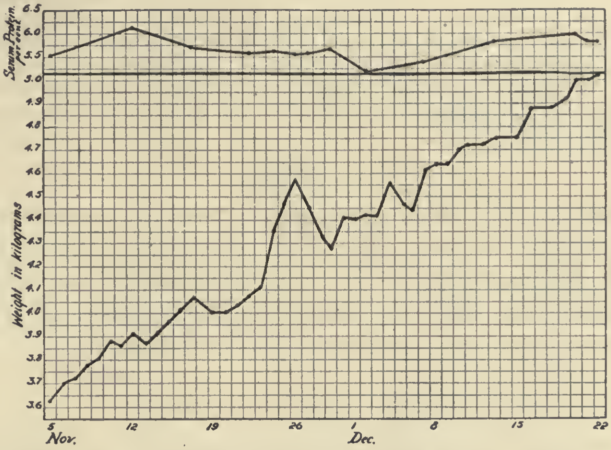


Chart 4.—Findings in Case 4.

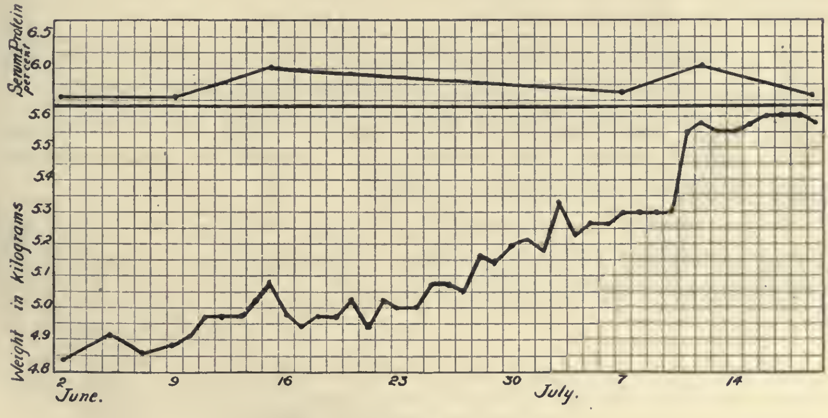


Chart 5.—Findings in Case 5.

Case 4 (Fig. 4).—H. M., a healthy boy, aged 2 months, was first observed, Nov. 5, 1920, when he weighed 3,630 gm. He was receiving a feeding consisting of 360 c.c. of whole milk, 90 gm. of lactose and 360 c.c. of water, on which he gained well. November 20, the milk in the feeding was increased to 450 c.c.

November 23, 100 gm. of maltose were substituted for the 90 gm. of lactose in the feeding. During the next three days the baby gained 470 gm., and in the following three days he lost 300 gm. During the period of rapid gain and loss, the serum protein concentration remained unchanged.

Case 5 (Fig. 5).—F. B., a healthy boy, aged 4 weeks, was admitted, April 9, 1920, when he weighed 3,970 gm.

June 2, when observations were started, he weighed 4,840 gm. and was receiving a feeding consisting of 420 c.c. of whole milk, 90 gm. of lactose and 390 c.c. of barley water, on which he gained slowly. June 19, the feeding was changed to 420 c.c. of whole lactic acid milk, 105 gm. of dextrimaltose and 390 c.c. of barley water. He did well on this until July 10, when, without change of feeding, he gained 250 gm. within twenty-four hours. During this twenty-four hour period he passed only 33 c.c. of urine.

Despite the marked gain in weight, no significant change in the serum protein concentration occurred, indicating that there was no increase in the water content of the plasma.

COMMENT

The effect of rapid gains in weight on the blood water was studied refractometrically in five cases. In no instance did a significant increase in the blood water occur. Since the increase in weight represents an increase in the water content of the organism, it seems clear that the increased amount of fluid is held in the tissues.

SUMMARY AND CONCLUSIONS

1. Freund has shown that marked variations in the weight curve of an artificially fed infant are due to changes in the water content of the organism.

2. Variations in the blood water were studied with the refractometric method in five babies before and after marked increases in weight.

3. Despite marked gains in weight (presumably due to an increase in the water content of the organism), no significant increase in the water content of the plasma occurred.

4. An increase in the amount of tissue fluid may occur in the healthy, artificially fed infant without a corresponding increase in the water content of the plasma.

BOOK REVIEWS

PREMATURE AND CONGENITALLY DISEASED INFANTS. By Julius H. Hess. Price, $5.50. Pp. 397, with 189 engravings. Philadelphia and New York: Lea & Febiger, 1922.

In this book the author presents the problem of the premature and congenitally diseased infant to the pediatrician, obstetrician and general practitioner. If these children are to be saved, preparations must be made beforehand, and every care used before, during and after delivery. While the mortality is, and always will be, high, still lives may be saved if precautions are taken. It is true that a number of these children may never progress normally; on the other hand, the author emphasizes the fact that some of them develop and may later be indistinguishable from those born at term.

The book consists of four parts. In the first, etiology, physiology and pathology are discussed. It contains many interesting and useful tables dealing with body weight and other measurements of the fetus. The author discusses heat regulation and points out that it is one of the least developed functions in the premature infant, and, therefore, special care must be taken to prevent hypothermia. He also gives a description of the various organs and illustrates, by means of pictures and tables, the changes that take place during development. Considerable space is given to discussion of the time of appearance of centers of ossification. He favors the roentgenographic method of determining the age of the fetus. This section is well illustrated by roentgenograms.

In Part II he enlarges on the nursing and feeding care. He dwells on the care of the mother, the choice of a wet nurse, diet for mothers, technic of nursing and of breast pressure. The author then emphasizes the chief points in the immediate care of the premature infant; giving plans of wards, with pictures of equipment and giving hospital records. The care of these children in the home, when they cannot be removed to the hospital, is also dealth with. Feeding is discussed at length, and a chapter is devoted to incubators.

General diseases observed in the premature infant are taken up fully by systems in Part III and are discussed, whenever possible, from the standpoint of etiology, morbid anatomy, symptoms, diagnosis, prognosis and treatment.

The outlook for the premature infant is dealt with in the last part.

The author covers his field thoroughly, and the work is intensely practical throughout.

SYPHILIS OF THE INNOCENT. By Harry C. Solomon, B.S., M.D., and Maida Herman Solomon, A.B., B.S., Washington: United States Interdepartmental Social Hygiene Board, 1922.

This book is a well written, concise résumé of syphilis as a family disease. All unnecessary detail is eliminated, and the essential facts are presented in a brief but interesting manner. The five chapters are well arranged, following one another in logical sequence. Statistics are worked up in as interesting a manner as their purpose will permit. Syphilis with its protean manifestations is found in all the branches of medicine, and to the specialist, as well as to the general practitioner, the disease presents scientific, social and economic problems. The book as a study of the social effects of syphilis on the family and the community, with a proper evaluation of these effects, is of interest to physicians, as well as to social workers.

CORRECTIONS

Dr. David M. Siperstein requests that attention be directed to two errors that occurred in his articles which appeared in the February and March issues of the American Journal of Diseases of Children. In the article in the February issue the subtitle of the caption of Table 9 should read "Blood Counts Following Hemorrhage," instead of "Blood Counts Following Injection." In the second article, which appeared in March, the erythrocyte counts in Table 2 should read: 4,160,000 and 4,280,000, instead of 5,160,000 and 5,280,000.

Dr. Dunn has called attention to an error in his article on "A Statistical Analysis of the Causes of Palpable Lymph Glands in the New-Born" in the April issue. On page 333, line 23, is a reference to Lippman which should read: "Thirteen of the babies had palpable inguinal glands. The normal leukocyte count established by Lippman was 16,600 at birth, 22,500 at 12 hours, 11,300 at 48 hours, and 9,500 by the fifth day of postnatal life."

Enables the physician to prescribe a nutritious and digestible diet that is thoroughly dependable.

For

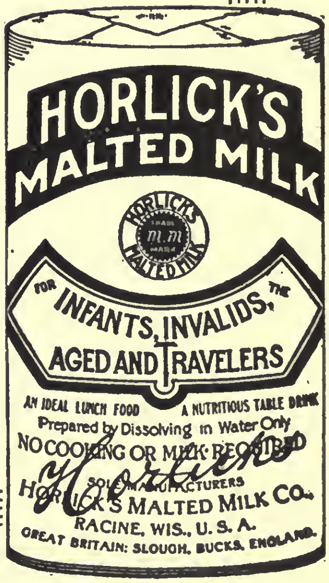
Expectant and
Nursing Mothers
Infants and
Growing Children

The quality and efficacy of "Horlick's" have won for it the confidence and endorsement of the medical profession.

Samples and literature
prepaid upon request

Ask for
"Horlick's the Original"
Avoid imitations

Horlick's Malted Milk Co.
Racine, Wis.



Pure
Maltose
—87.4%—
for
Infant
Feeding

BORCHERDT'S
MALT SUGAR
CONTAINING APPROXIMATELY
MALTOSE 87%
DEXTRIN 5%
MAKES PRACTICAL THE USE OF
MALTOSE
WHEREVER INDICATED AS AN ADJUNCT TO INFANT FEEDING
SPECIFICALLY INDICATED IN THE
CONSTIPATION
OF INFANTS
PREPARED BY THE
Borcherdt Malt Extract Co.
CHICAGO ILL.

BORCHERDT'S MALT SUGAR

Solving Many Problems of Infant Feeding

This preparation makes possible and practical the use of Maltose in any proportion which the condition of the individual child may indicate. Requiring little, if any digestion, Borcherdt's Malt Sugar may be easily tolerated by those infants who have not responded to other preparations.

Correcting Constipation Difficulties

The high percentage of Maltose permits a quick and definite adjustment of diet to overcome constipation. When the large number of complications that can result from constipation are considered the usefulness of Borcherdt's Malt Sugar as a corrective will not be minimized by the pediatrician.

Send for Samples, Literature, Analysis

Correspondence from physicians is appreciated. Let us send you a sample can so that you may personally examine this product.

BORCHERDT MALT EXTRACT COMPANY
217 North Lincoln Street
Chicago, Illinois

Pillsbury's
Wheat Cereal

In order that you may know, at first hand, the real superiority of Pillsbury's Wheat Cereal, we gladly send to doctors, without charge, a full size package of this pure farina product.

Test it on your own table, or get a patient's verdict. Note especially its richness and *smoothness* when cooked. Because of its uniform granulation, Pillsbury's Wheat Cereal does not lump, when cooked according to directions on package.

Every step in the preparation of Pillsbury's Wheat Cereal, from the scientific selection of wheat to packing in air-tight containers, is completely handled by the Pillsbury Flour Mills Co. Thus we *know* and can *guarantee* what goes into it. And it's untouched by human hands. Request a package from us today.

PILLSBURY FLOUR MILLS COMPANY
MINNEAPOLIS, U. S. A.

Pillsbury's Family of Foods
Pillsbury's Best Flour · Pancake Flour · Wheat Cereal · Health Bran
Rye Flour · Durum Flour · Farina

SPECIAL DRY MILK FOR BABIES
INVALIDS and CONVALESCENTS

MAMMALA

100% PURE MILK SOLIDS IN EASILY ASSIMILABLE FORM

It is simply pure fresh cow's milk of the best quality, modified for Babies, Invalids and Convalescents by removing a part of its cream and by adding a suitable proportion of milk-sugar, and then dried rapidly by the scientific process of HATMAKER, which kills all disease germs that may be present and renders the milk safe and highly suitable for Baby and Invalid feeding. It is composed entirely of milk constituents and does not contain any starch, malt, cane-sugar, bi-carbonate of soda or other foreign substance.

REDUCTION IN PRICE (as below)

MAMMALA can be obtained direct from the Model Dairy where it is made, by Parcel Post, postpaid, by remitting 85 cents for a small-size or $5.00 for a large-size box, by check or Money Order to the

MAMMALA CORPORATION, Knoxville, Tioga Co., Pa. ***Or from first class Druggists***

Larosan
"Roche"

A DAY'S FEEDING CAN BE
PREPARED BY THE MOTHER
IN A FEW MINUTES

THE ORIGINAL
CALCIUM CASEINATE
SO SUCCESSFULLY AND WIDELY
USED IN THE MANAGEMENT OF
FERMENTATIVE DIARRHEAS
AND
NUTRITIONAL DISORDERS
OF
INFANTS AND CHILDREN

Reprints and abstracts of Medical articles on application

The Hoffmann-La Roche Chemical Works, New York

American Journal of Diseases of Children

Vol. 25 JUNE, 1923 No. 6

THE IMPORTANCE OF COLOSTRUM TO THE NEW-BORN INFANT *

ANN KUTTNER, Ph.D.
AND
BRET RATNER, M.D.
NEW YORK

The recent work of Smith and Little has definitely shown the importance of colostrum to the new-born calf. Not only is colostrum, according to Smith and his co-workers, the chief agent for transferring known antibodies to the new-born calf, but it seems to have also the important function of protecting the new-born animal of this species against a general invasion by organisms of the *B. coli* group which find their way into the intestinal tract during the first few days of life. These experiments which show so strikingly the value of colostrum to the new-born calf have again raised the question of the importance of colostrum to the human species.

SUMMARY OF RECENT WORK ON THE IMPORTANCE OF COLOSTRUM TO ANIMAL AND MAN

The concrete additions to our knowledge of the function of colostrum, made by Theobald Smith and his collaborators at the Rockefeller Animal Experiment Station, are as follows:

1. Little and Orcutt[1] have shown that calves born of cows which have become highly immune to *B. abortus* in the course of a natural infection with this organism have no agglutinins in their serums at birth. After the ingestion of colostrum, agglutinins appear in the serum of the calf and usually equal or even surpass the titer of the cow.
2. Howe[2] has shown that the blood of the new-born calf before the ingestion of colostrum is lacking both in pseudoglobulin and euglobulin. After the ingestion of colostrum, the globulin content rises rapidly as compared with that of the serum of calves that fail to receive colostrum.
3. Smith and Little[3] have shown that calves that fail to obtain colostrum succumb in from 75 to 80 per cent. of the cases to a generalized *B. coli* septicemia. In this experiment, the control colostrum-fed calves that were allowed to nurse for a very short time immediately after birth (fifteen minutes

---

* Received for publication, April 25, 1923.

* From the Department of Bacteriology and the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University.

[1] Little, R. B., and Orcutt, M. L.: J. Exper. Med. **35**:161-171 (Feb.) 1922.

[2] Howe, P. E.: J. Biol. Chem. **49**:115 (Nov.) 1921.

[3] Smith, Theobald, and Little, R. B.: J. Exper. Med. **36**:181-198 (Aug.) 1922.

in one instance) survived; which indicates that a relatively small amount of colostrum is sufficient to prevent the invasion of *B. coli* in these animals.

4. In a subsequent paper, Smith and Little[4] have demonstrated that cow's serum may be substituted for colostrum.

In the various papers published by Theobald Smith and his co-workers, the conditions discovered by them in calves were not applied to the human species.

Interesting observations bearing on this subject have recently been published by Williams.[5] He finds that scours in the new-born calf is best avoided if the animal is allowed to nurse in the normal way. He assumes that this is due to antibodies present in the mammary secretion. (Williams does not differentiate between colostrum and milk.) This observer, however, maintains that the infection of the new-born calf which leads to fatal diarrhea takes place in utero instead of after birth, and the milk is of value largely because, in the course of the uterine infection, the mother has acquired a considerable increase of specific antibodies.

The work of Little and Orcutt, demonstrating the importance of colostrum in the transference of agglutinins to the new-born calves, was a corroboration of a similar series of experiments performed by Famulener[6] with goats in 1912. Famulener was the first investigator to emphasize the value of colostrum. His work differed from that of Little and Orcutt in that the goats used by him were artificially immunized with red blood cells during the course of pregnancy. He showed that the kids were born without hemolysins in their serum, and depended solely on the colostrum for transmission of these antibodies. In summing up his article, Famulener, from his work on goats, concluded that colostrum is equally important to the infant:

> It follows from our observations that of all factors the colostrum plays the most important rôle in transmitting antibodies from the actively immunized mother to the young. Even under normal conditions, it is reasonable to suppose that protective substances are concentrated from the mother's body fluids and may be absorbed by the infant after the first feedings. Consequently, it seems of the highest importance that the newly born child should, during the first few days of life, receive the colostrum-milk unless contraindicated for some special reason.

Lewis and Wells,[7] in a recent article, have tried to determine the function of colostrum in the human species by a study of new-born infants.

They studied the globulin content of six different specimens of cord blood and found that, in contrast to the calf, the infant is born with a normal amount of pseudoglobulin, and is lacking only in euglobulin. They investigated the globulin content of the serum of three new-born infants after the ingestion of colostrum and found a definite rise in the euglobulin as compared with the serum of one infant that had not been fed with colostrum. From these experiments, Lewis and Wells conclude that colostrum is also of great importance to the human species, since in their opinion, euglobulin is "the predominent protein of colostrum," and "is unique in its association with immune bodies."

---

[4] Smith, Theobald, and Little, R. B.: J. Exper. Med. **36**:453-468 (Oct.) 1922.

[5] Williams, W. L.: Am. J. Obst. & Gynec. **4**:513 (Nov.) 1922.

[6] Famulener, L. W.: J. Infect. Dis. **10**:332-368 (May) 1912.

[7] Lewis, J. H., and Wells, H. G.: Function of Colostrum, J. A. M. A. **78**:863-865 (March 25) 1922.

Boyd[8] has recently corroborated the findings of Lewis and Wells.

Ten different specimens of cord blood which she analysed were normal as to pseudoglobulin, but showed marked deficiency of euglobulin. Seven infants in these cases showed a definite rise of the euglobulin fraction after the ingestion of colostrum; whereas, the remaining three, who did not receive colostrum, showed a diminished amount of euglobulin.

THE RELATION OF THE STRUCTURE OF THE PLACENTA IN VARIOUS ANIMAL SPECIES TO THE TRANSFERENCE OF IMMUNE SUBSTANCES FROM MOTHER TO OFFSPRING

The studies of Howe on the globulin content of the serums of new-born calves before the ingestion of colostrum, on the one hand, and those of Lewis and Wells, and Boyd, on specimens of human cord blood on the other, show a difference in the permeability of the human and bovine placentas. Thus, in Howe's experiments, the cow's placenta was definitely impermeable to both euglobulin and pseudoglobulin. Lewis and Wells and Boyd agree that the human placenta allows the passage of pseudoglobulin in undiminished quantity, and only euglobulin is held back.

All the evidence cited above seems to indicate that colostrum plays an important rôle in transferring immunity from mother to offspring. These recent experiments are difficult to reconcile with some of the findings of the older investigators who give definite evidence for both placental and milk transmission. Theobald Smith[9] suggested that although he and his co-workers had found that colostrum was of unquestionable importance to the new-born calf, it was his opinion that the same conditions probably did not prevail in other species, and that the factor determining the difference might be found in the structure of the placenta. With this point of view in mind, we sought evidence of histologic differences in the placentas of various species. Grosser[10] who made a comprehensive study of the placenta of different animals has shown that the number of cell layers separating the maternal from the fetal circulation varies according to species, as indicated in Table 1.

---

8. Boyd, G. L.: Canad. M. A. J. **12**:724 (Oct.) 1922.
9. Smith, Theobald: Personal Communication.
10. Grosser: Eihäute and Placenta, Vienna and Leipzig, Braumüller, 1909.

The fact that in the human placenta the maternal blood is separated from the fetal by only a single cell layer, whereas, in the case of ruminants, the placenta consists of three cell layers, would seem to indicate a physical basis for the difference in permeability of the bovine and human placentas to globulins as shown by Howe's work on the new-born calf, by that of Lewis and Wells, and by Boyd's on human cord blood. Furthermore, it seemed possible that the differences in the permeability of the placenta in the different animal species, shown by Grosser's chart, might account for some of the discrepancies in the results of various experimenters in the past who have studied the transference of immunity. Thus, some workers claim that the placenta is impermeable to antibodies and that the milk is the only means of transferring immunity to the young. Others insist that the placenta is permeable and that the placental transmission is the most important mode of transferring antibodies. In analyzing the literature from this point of view, we found a striking conformity of results when cows, horses, goats and sheep were the experimental animals, and a similar correspondence of results when the work was done on human beings, rabbits, guinea-pigs and mice. But there were marked discrepancies between the findings with the former and with the latter groups of animals.

TABLE 1.*—*Variations in Cell Layers Separating Maternal From Fetal Circulation*

		Partition Between Maternal and Fetal Blood								
		Maternal (Uterine Mucosa)				Fetal (Chorion)				
Nomenclature										
Old	New	Endothelium	Connective Tissue	Epithelium	Uterus Cavum	Endothelium	Connective Tissue	Epithelium	Types	Remarks
Semiplacentae or Placentae oppositae	Placentae epitheliochorialis	+	+	+	+	..	+	..	Pig	True adeciduate
	Placentae syndesmochorialis	+	+ Partly	— Mostly	—	..	+	..	Ruminants	Transition forms
Placentae verae or Placentae conjugatae	Placentae endotheliochoriolis	+	— Almost entirely	—	—	..	+	..	Carnivora	Placentae zonariae (deciduate)
	Placentae haemochorialis	—	—	—	—	..	+	..	Rodentia Insectivora Chiroptera Apes Man	Placentae discordales (deciduate)

* Grosser: Eihäute und Placenta, p. 292.

The majority of workers, such as Ehrlich,[11] Merkel,[12] Stäubli,[13] Jurewitsch,[14] Dieudonné,[15] Polano,[16] Schumacher,[17] etc., who worked

---

11. Ehrlich, P.: Ztschr. f. Hyg. u. Infectionskrankh. **12**:183, 1892.
12. Merkel, H.: München. med. Wchnschr. **8**, 1904.
13. Staübli: Centralbl. f. Bakteriol. **36**:291, 441, 1904.
14. Jurewitsch: Centralbl. f. Bakteriol. **33**:76, 1903.
15. Dieudonné: Cited by Pfaundler.
16. Polano: Ztschr. f. Geburtsh. u. Gynäk. **53**:456, 1904.
17. Schumacher: Ztschr. f. Hyg. u. Infectionskrankh. **37**:323, 1901.

on guinea-pigs, rabbits or man, agreed that the placenta was permeable to antibodies. Roemer,[18] Famulener,[6] Little and Orcutt[1] and others who worked mainly with cows, goats, horses and sheep found the placenta impermeable. Roemer is one of the few investigators who worked with animals of two placental types. In his experiments, the placenta of cows, sheep and horses were uniformly impermeable to antibodies; whereas, with guinea-pigs, rabbits and human beings, he, in practically every instance, found that the antibodies were transmitted through the placenta, though usually in diminished amount.

Bourquin[19] has recently confirmed the permeability of the placentas of guinea-pigs and rabbits to diphtheria antitoxin, hemolysins and agglutinins. An interesting feature of her work is that she examined the placenta in every instance and found no gross lesions.

The conception of the earlier investigators, as represented by the school of Behring, Pfaundler and Roemer, was that the placenta, irrespective of the animal species, was impermeable to proteins and did not permit the passage of maternal antibodies. In their opinion, antibodies only appeared in the fetal blood if the placenta was injured either through disease or by heterologous proteins, such as horse serum antitoxin used in the course of the experiments. Placental transmission of antibodies was, therefore, in their opinion, a pathologic and not a physiologic process.

The opinion that placental injury due to horse serum antitoxin injection determined placental permeability has been conclusively contradicted by a number of workers. They excluded this possibility by immunization of the mother before conception (Stäubli), and by studies on the transference of natural immunity when no injections of any kind were practiced on the mother (Polano). The theory of placental transmission of immune bodies due to injury has, therefore, become untenable.

It seems probable to us that the histologic differences in the structure of the placentas of the various species might sufficiently explain the varying results obtained. In the cases in which the placenta consists of a single layer, as in rodents, apes and man, the greatest degree of permeability has been experimentally observed, and this contrasts strongly with the conditions found among the ruminants. The fallacy of applying facts discovered in one animal species to another is thus indicated.

CONFIRMATION OF THE PERMEABILITY OF THE HUMAN PLACENTA TO DIPHTHERIA ANTITOXIN

In approaching this problem of the permeability of the human placenta to diphtheria antitoxin experimentally, we decided to study the conditions of placental permeability to diphtheria antitoxin in preference to other antibodies because of the ease and accuracy with which this antibody lends itself to quantitative determination.

---

[18] Roemer: Beitr. z. exper. Therap. **9,** 1905.

[19] Bourquin, H.: Am. J. Physiol. **59**:122 (Feb.) 1922.

Historical.—Fischl and Wundscheim[20] were the first investigators to demonstrate diphtheria antitoxin in a large proportion of specimens of cord blood examined by them.

Polano[16] studied the passive transfer of diphtheria antitoxin from mother to child in women who were naturally immune. He was able to demonstrate antitoxin in the cord blood in every case.

Von Groer and Kassowitz[21] made a more extensive study of the same subject. In 84 per cent. of their cases, the cord blood and the maternal blood were identical as to antitoxin content, as titrated by the Roemer method. They conclude that, since they found antitoxin in the cord blood in such a large percentage of cases, the human placenta is normally permeable to diphtheria antitoxin. These investigators found that the Schick reaction did not regularly coincide with the antitoxic content of the maternal serum; but, since they omitted the usual Schick control, their observations cannot be considered conclusive. They made the observation that, in 11.2 per cent. of their cases, when the absence of antitoxin had been demonstrated in the cord blood, they failed to obtain positive Schick reactions in the new-born infant.

Zingher[22] also performed comparative Schick tests, on a series of twenty-three mothers and infants. He found that, with infants under 3 months of age, the Schick reaction in mother and child corresponded in every case except one. Since he did not include any antitoxin determination on the cord bloods and made no Schick tests on infants before they had nursed, it was not clear from his work whether the placenta or the colostrum was the most important agent in transmitting diphtheria antitoxin.

Ruh and McClelland[23] have recently studied a larger series of cases. The infants were all less than 7 days old. Ninety-five mothers and their babies gave corresponding reactions. Seventy-five reactions were negative and twenty positive. In four cases, the mothers gave positive reactions and their babies negative. In only a single instance was a positive reaction obtained in a baby when the mother's reaction was negative. In eight of the cases, Schick tests were performed on infants before they had nursed. Thus the two factors, placental and mammary transmission, could be judged separately. It was found that when the mother gave a negative Schick reaction, the reaction of the infant was negative before the ingestion of colostrum.

Experimental Work.—This included:

1. Determination of the presence of antitoxin in maternal and cord blood by the Kellogg method in mothers giving Schick negative and positive reactions.
2. Comparative Schick reactions in mothers and newly born infants.
3. Determination of any loss of antitoxin by passage through the placenta.

---

20. Fischl and Wundscheim: Ztschr. f. Heilk. **16**:429, 1895.

21. Von Groer and Kassowitz: Ztschr. f. Immunität. u. exper. Therap. **23**:108, 1914.

22. Zingher, Abraham: Further Studies in the Schick Test, Arch. Int. Med. **20**:392 (Sept.) 1917.

23. Ruh, H. C., and McClelland, J. E.: Comparison of Diphtheria Inmmunity in the Mother and in the New-Born, Am. J. Dis. Child. **25**:59 (Jan.) 1923.

Procedure: (*a*) Schick tests were performed on women attending the Sloane Clinic anywhere from one week to three weeks antepartum. At the same time, a specimen of blood was taken. The material for the Schick tests was obtained through the courtesy of the Research Laboratory of the New York City Department of Health. The test was performed according to directions, a control injection of heated toxin being made in every case. Readings on the Schick reaction were made after forty-eight hours, and again after several days.

(*b*) Specimens of cord blood were collected from patients with positive Schick reactions, as well as from those with negative reactions.

(*c*) Comparative determinations for the presence or absence of diphtheria antitoxin in the maternal and the cord blood were made according to the method recently described by Kellogg.[24]

Kellogg's method: Kellogg bases his procedure on the findings of Schick to the effect that a negative Schick reaction indicated at least one-thirtieth antitoxin unit for each cubic centimeter of blood. The L + dose of toxin is diluted in 30 c.c. of saline, so that each cubic centimeter contains one thirtieth of the L + dose. This toxin dilution is then combined with an equal amount of the serum, to be tested and allowed to stand at room temperature for thirty minutes; and 0.2 c.c. is then injected intracutaneously into the shaved skin of a white guinea-pig, this representing one three-hundredth L + dose, together with whatever antitoxin may be contained in 0.1 c.c. of the serum to be tested.

Table 2.—*Results of Tests of Maternal and Cord Blood*

Total Number of Cases	Schick Reaction on Mothers		Kellogg Method	
	Positive	Negative	Maternal Blood	Cord Blood
30	11	19	11+[*]	11+
			19—	19—

[*] + indicates a positive skin reaction in the guinea-pig, showing less than one-thirtieth antitoxin unit per cubic centimeter of serum tested; — indicates the absence of a reaction in the guinea-pig showing that the serum contained at least one-thirtieth antitoxin unit per cubic centimeter.

Thus, if the patient's serum contains more than one-thirtieth unit of antitoxin for each cubic centimeter, this amount of toxin will be completely neutralized, and no reaction will occur. If the patient's serum contains exactly one-thirtieth unit of antitoxin for each cubic centimeter, it means that one three-hundredth of a minimal lethal dose of diphtheria toxin is left unneutralized, and a slight reddening which never develops into necrosis will occur. If the patient's serum contains less than one-thirtieth unit, reddening and induration, later developing into definite superficial necrosis, result. The readings are best made after from forty-eight to seventy-two hours. Large pigs, weighing from 400 to 500 gm. give the most nearly uniform results.

1. *Determination of the Presence of Antitoxin in Maternal and Cord Blood by the Kellogg Method in Mothers Giving Negative Schick Reactions and in Those Giving Positive Reactions.*—We studied a total of thirty cases in this way. None of the women included in our series gave a history of diphtheria. The results are recorded in Table 2.

Results: Table 2 shows that, in all cases, in which a negative Schick reaction was obtained on the mother, both the maternal serum and the cord blood contained a sufficient amount of antitoxin to give a

---

24. Kellog, W. H.: A Test for Diphtheria Immunity and Susceptibility, J. A. M. A. **78**:1782-1783 (June 10) 1922.

negative Kellogg reaction on the guinea-pig. In the thirty cases tested by us, we have found that the Schick reaction coincided in every instance with the result obtained by the Kellogg method. In the nineteen mothers giving a negative Schick reaction, we were able to demonstrate the presence of antitoxin in the cord blood in every case. The cord blood obtained from Schick positive cases in no instance contained antitoxin.

2. *Comparative Schick Reactions in Mothers and New-Born Infants.*—We included a series of fifty comparative Schick tests on mothers and infants in our study to see whether we could obtain any information as to the discrepancies reported by previous workers in regard to Schick reactions on the new born. All the infants tested by us were less than 14 days old and were colostrum fed.

Results: The results recorded in Table 3 agree with the findings of others that mothers having Schick negative reactions give birth to infants having negative reactions, and that the new-born give no pseudoreactions. In Schick positive cases, on the other hand, the reaction in mother and child does not, as noted by previous workers, correspond in every case. In our series a large proportion of the infants born of mothers with positive Schick reaction gave either a negative or an extremely doubtful reaction.

TABLE 3.—*Results in Comparative Schick Tests*

Total Number of Cases	Reactions of Mother and Baby Negative	Reactions of Mother and Baby Positive	Positive Reaction in Mother; Negative or Doubtful Reaction in Baby	Negative Reaction in Mother and Positive in Baby	Pseudoreactions in This Series	
					Mothers	New-born Babies
50	39	4	7	0	10	0

Ruh and McClelland attribute this discrepancy to the peculiar character of the skin of the new-born. They found that greater pressure was required to make an intradermal injection in an infant's skin, and that with the same technic as that used for adults the wheal produced was smaller and disappeared more rapidly.

The difficulties encountered by Ruh and McClelland in performance of the Schick test on infants are in accord with our experience. The failure to obtain positive reactions with regularity in infants is probably due to the fact that the toxin diffuses and is not held within the layers of the skin for a sufficient length of time to obtain a definite local reaction. In order to prove that the failure to obtain a positive Schick reaction was entirely due to the peculiar physical character of the skin of the new-born, we tested the cord blood of six of the seven infants in our series, born of mothers giving

Schick positive reactions and themselves giving a negative or a doubtful reaction, and found a deficiency in antitoxin in every one of these cases when tested by the Kellogg method.

The reactions in the four infants that gave Schick positive reactions were much less definite than those obtained in their respective mothers. The reactions in these new-born infants usually reached their height in twenty-four hours, and the test area then faded rapidly, leaving practically no discoloration except in the colored infants, so that at the end of forty-eight hours the test often appeared negative.

Table 4.—*Comparison of Antitoxin Content of Maternal and Cord Blood*

Case	Dilution of L+ Dose in 0.1 C.c.*	Maternal Serum	Cord Blood Serum	Unit per C.c. of Maternal Blood	Unit per C.c. of Cord Blood
1	1/100†	—	—		
	1/50	+	+	1/10†	1/10†
2	1/50	—	—		
	1/25	+	+	1/5	1/5
3	1/50	—	—		
	1/25	+	+	1/5	1/5
4	1/25	—	—		
	1/10	+	+	2/5	2/5
5	1/15	—	—		
	1/10	+	+	2/3	2/3
6	1/50	—	—		
	1/25	+	+	1/5	1/5
7	1/150	—	—		
	1/100	+	+	1/15	1/15
8	1/50	—	—		
	1/25	+	+	1/5	1/5
9	1/50	—	—		
	1/25	+	+	1/5	1/5
10	1/25	—	—		
	1/10	+	+	2/5	2/5
11	1/15	—	—		
	1/10	+	+	2/3	2/3
12	1/150	—	—		
	1/100	+	+	1/15	1/15
13	1/15	—	—		
	1/10	+	+	2/3	2/3

* Actual amount of toxin expressed in fraction of L+ dose.

† Calculations from these measurements were based on the following reasoning: The work of Kellogg, confirmed by us, showed that one three hundredth of the minimal lethal dose of toxin is the smallest amount of toxin that will give a definitely determinable skin reaction, characterized by redness with some induration and subsiding without necrosis. The smallest amount of toxin that will produce a definite necrosis is one fortieth of the minimal lethal dose. Since only Schick negative cases were studied quantitatively, we knew that 0.1 c.c. of all these serums would neutralize at least one three hundredth of the L+ dose. In order to establish the limit of antitoxin content in any particular specimen of blood, a constant amount of serum, 0.1 c.c., was combined with increasing fractions of the L+ dose. The amounts of toxin used in these determinations varied from one one hundred and fiftieth of the L+ dose to one-tenth of the L+ dose. The limits of the neutralizing action of each serum were thus reached, as shown in the chart, the minus sign indicating the largest amount of toxin that gave no reaction at the site of inoculation on the skin of the guinea-pig, and the plus sign a definitely positive skin reaction usually going on to necrosis. The amount of antitoxin per cubic centimeter was thus calculated as follows: In Case 1 in Table 4, 0.1 c.c. of serum plus one one hundredth L+ dose was negative. The serum, therefore, contained one-tenth or more antitoxin units per cubic centimeter, but not much more, since the same amount of the same serum mixed with one-fiftieth L+ dose gave a positive reaction. It, therefore, must have contained more than one-tenth, but less than one-sixth, unit of antitoxin.

From our results, as well as from those obtained by other workers, it seems apparent that the Schick test on the new-born infant is unreliable. The immunity or susceptibility of the new-born infant to diphtheria can therefore be determined with accuracy only by performing a Schick test on the mother or by showing the presence or absence of antitoxin in the cord blood or the infant's blood by the Kellogg method.

3. *Determination of Any Loss of Antitoxin by the Passage Through the Placenta.*—It was the opinion of the older investigators, particularly Roemer, that, even if a certain amount of immune substance did pass through the placenta, the titer of the offspring was always definitely less than that of the mother. It seemed worth while, therefore, to see how the antitoxin content of the maternal and the cord blood compared by accurate titrations according to the Roemer method.

Method: Equal quantities of the serums obtained from the mother's blood and the cord blood were mixed with increasing concentrations of toxin and allowed to stand for thirty minutes at room temperature; 0.2 c.c. amounts were then injected into large white guinea-pigs. Titrations were made until a point was reached at which the antitoxin in the serum failed to neutralize the toxin, and in consequence a skin reaction was obtained, as shown in Table 4. Most of the titrations were repeated several times before a final conclusion was reached.

Results: Table 4 shows that, in the thirteen cases in which the antitoxin content was titrated in maternal and in cord blood, there was no loss of antitoxin by passage through the placenta. Our results agree with those of von Groer and Kassowitz, who also found the titer of antitoxin identical in a large number of specimens of maternal and cord blood.

OBSERVATIONS ON THE RÔLE PLAYED BY COLOSTRUM IN THE TRANSFER OF DIPHTHERIA ANTITOXIN IN HUMAN BEINGS WHEN THE PLACENTA IS KNOWN TO BE PERMEABLE TO ANTITOXIN

In the studies reported above, we have confirmed the observations of a number of other workers in showing conclusively that the human placenta is permeable to diphtheria antitoxin, and it seems likely that this permeability is causally related to the histologic conditions prevalent in human beings, who may be classified on this basis with the placentae verae group.

Colostrum cannot, therefore, be regarded as the sole means of transmission of antitoxic immunity in man. Nevertheless, we believed it important to investigate the possible participation of the colostrum in this process by direct experiment.

1. *Determination of the Presence of Antitoxin in Colostrum of Schick Negative Mothers.*—We attempted to determine the presence of diphtheria antitoxin in the colostrum by means of skin tests, using methods identical with those employed in the case of serum. We found that the control injections of colostrum alone were not readily absorbed and they produced a certain amount of induration which made accurate readings impossible. These irritating effects of the colostrum could be almost entirely eliminated by centrifugalizing, removing the supernatant layer of fat, and corpuscles, and injecting

the clear fluid below. Experiments with this clear fluid were e negative. No neutralizing effect was observed with any of the centrifugalized specimens of colostrum tested by us.

The failure to demonstrate antitoxin in the colostrum by the intradermal method seemed to indicate the absence of antitoxin in the colostrum of women giving Schick negative reactions. The studies of previous workers on the antitoxin content of the milk of highly immunized animals showed that the titer of the mammary secretion is always markedly less than that of the blood. It, therefore, seemed possible that antitoxin in human colostrum might be present in very small amounts which could not be readily demonstrated by the intradermal method. We therefore determined to abandon the intradermal method in favor of direct measurements of the protective effect of colostrum by intraperitoneal injection into guinea-pigs.

The only available reports on the antitoxin content of the milk of women naturally immune to diphtheria in which protection tests were employed are those of Pflanz and Schmidt.[25]

They did not examine the colostrum, but studied the milk in six cases during a period of from four to thirty days after delivery. The work of these investigators indicates that the antitoxin content of milk is always from one-tenth to one twenty-fifth less than that of the cord blood, but their experiments do not seem to us reliable, since they used exceedingly small amounts of toxin; namely, 1 minimal lethal dose, combined with relatively large amounts, from 1 to 5 c.c., of milk, mixing the two before injection.

It appeared to us that any method in which milk or colostrum was mixed with toxin before injection might introduce a source of error connected with the possible nonspecific adsorption of toxin by lipoidal and other substances in the milk. Moreover, the employment of simultaneous or of subcutaneous injections appeared fraught with possible error, owing to slow absorption due to the viscid nature of colostrum. For this reason, in order to create conditions most favorable to any possible protective effect on the part of the colostrum or milk, we carried out the experiments by injecting these substances intraperitoneally, twenty-four hours before the toxin was administered. This insured the presence of a maximum number of any protective bodies in the circulation at the time that the dose of toxin was given. All our experiments were controlled by parallel injections of toxin alone. In order to avoid any possibility of nonspecific effects, moreover, the injections of colostrum from women giving negative Schick reactions were in some cases paralleled by intraperitoneal injections of colostrum from women giving Schick positive reactions or of blood serum from Schick positive cases injected into guinea-pigs.

---

[25] Pflanz and Schmidt: Wien. klin. Wchnschr. **42**:955, 1896.

Experimental Work.—It was important in making these estimations to be able to differentiate between colostrum and milk, since we were mainly interested in obtaining information as to the rôle played by colostrum in transferring diphtheria antitoxin. We therefore classified the mammary secretion obtained in the course of our experiments according to the following criteria:

Colostrum: This was defined as the secretion expressed from forty-eight to sixty hours postpartum, which coagulated on boiling and showed the presence of large numbers of colostrum corpuscles under the microscope.

Transitional milk: This was defined as a slightly yellowish secretion obtained from twelve to eighty hours postpartum, which did not coagulate on boiling but still showed a fair number of colostrum corpuscles.

Milk: This was obtained usually on the fourth day postpartum and thereafter. It did not coagulate on boiling and showed none or very few colostrum corpuscles.

Method: Colostrum in quantities ranging from 1 to 8 c.c. obtained from women giving a negative Schick reaction was injected intraperitoneally into guinea-pigs weighing from 250 to 300 gm. At the same time, 1 c.c. of the serum of the cord blood from the same case was also injected intraperitoneally into pigs of similar weight.

In some of our early experiments, control guinea-pigs were injected with colostrum obtained from women giving a positive Schick reaction, but since no protection was ever obtained in this way, this method was abandoned, and the control animals were usually injected with 1 c.c. of serum from a Schick positive case. The toxin was subcutaneously injected, twenty-four hours later. The amount used in our earlier experiments was 1 c.c. of diluted toxin corresponding to one-thirtieth L dose. With this amount, however, the animals lived for as long as from seven to fourteen days. In later experiments, one-fifteenth L + dose was subcutaneously injected in a total volume of 1 c.c., since we found that this amount killed animals weighing from 250 to 300 gm. in from forty-eight to seventy-two hours. When pigs weighing more than 300 gm. were employed, one-tenth L + dose was the amount injected.

In planning the experiments, the heavier pigs were always selected for the colostrum protection experiments in order to throw all the possibility of experimental error on the negative side. Necropsies were performed on all the animals that died, and an experiment was always considered invalid if any pathologic condition other than that due to diphtheria was revealed at necropsy. In the large majority of cases, the typical lesions of diphtheria, enlargement and congestion of the suprarenal glands, edema and necrosis at the point of injection, etc., were found. In a small number of animals, these signs were not typical, but in these, careful necropsy examination revealed no other possible cause of death. All the surviving pigs were kept under observation for at least one month.

By this method, we examined twenty specimens of colostrum. The results of these examinations are detailed in Tables 5 and 6.

Results: The results presented in Table 5 may be summarized thus: In nine of the cases reported, 1 c.c. of the serum obtained from the cord blood protected completely against the amount of toxin used, while in all but one of these cases the colostrum was entirely ineffective even with the largest amount used. In Case 4, the pig injected with

TABLE 5.—*Results of Protection Tests with Colostrum and Cord Blood*

	Colostrum						Cord Blood					Controls			
Case	Hours Post-partum	Amount Injected Intraperi-toneally, C.c.	Pig	Weight, Gm.	1 C.c. Toxin Subcu-taneously	Result	Amount Injected Intraperi-toneally, C.c.	Pig	Weight, Gm.	1 C.c. Toxin Subcu-taneously	Result	Pig	Weight, Gm.	1 C.c. Toxin Subcu-taneously	Result
1	48	2	A591	275	1/15 L+	Death, 48 hrs.	1	A588	250	1/15 L+	Discharged	A598	275	1/15 L+	Death, 48 hrs.
	48	6	A590	275	1/15 L+	Death, 48 hrs.									
2	48	2	A677	280	1/15 L+	Death, 72 hrs.	1	A675	230	1/15 L+	Discharged	A688	240	1/15 L+	Death, 72 hrs.
3	48	1	A499	275	1/15 L+	Death, 48 hrs.	1	A535	230	1/15 L+	Discharged	A689	240	1/15 L+	Death, 72 hrs.
	48	3	A686	270	1/15 L+	Death, 72 hrs.									
4	48	1	694	315	1/10 L+	Death, 96 hrs.	1	692	285	1/15 L+	Discharged	685	295	1/10 L+	Death, 48 hrs.
	48	4	499	205	1/10 L+	Discharged									
5	70	1	677	315	1/10 L+	Death. 48 hrs.	1	680	275	1/10 L+	Death, 96 hrs.	686	295	1/10 L+	Death, 48 hrs.
	70	4	687	310	1/10 L+										
6	66	2	186	275	1/15 L+	Death, 72 hrs.	1	691	240	1/15 L+	Discharged	675	245	1/15 L+	Death, 72 hrs.
	66	2	695	250	1/15 L+										
7	53	8	529	375	1/10 L+	Death, 72 hrs.	1	526	325	1/10 L+	Discharged	A535	335	1/10 L+	Death, 72 hrs.
8	57	4	692	245	1/15 L+	Death, 72 hrs.	1	676	235	1/15 L+	Death, 10 days	693	240	1/15 L+	Death, 48 hrs.
9	48	4	682	265	1/15 L+	Death, 72 hrs.	1	681	255	1/15 L+	Discharged	697	260	1/15 L+	Death, 48 hrs.
10	56	6	A191	290	1/15 L+	Death, 96 hrs.	1	A186	275	1/15 L+	Death, 8 days	281	280	1/15 L+	Death, 72 hrs.
11	48	4	535	305	1/10 L+	Death, 72 hrs.	1	532	285	1/15 L+	Discharged	538	295	1/10 L+	Death, 48 hrs.
												522	275	1/10 L+	
12	24	2	307	260	1/30 L+	Death, 5 days	1	A465	260	1/20 L+	Discharged	282	260	1/30 L+	Death, 7 days
	24	5	158	255	1/30 L+	Death, 72 hrs.						A468	255	1/30 L+	Death, 15 days

TABLE 6.—*Results of Protection Tests with Colostrum and Cord Blood*

	Colostrum						Cord Blood					Controls			
Case	Hours Post-partum	Amount Injected Intraperi-toneally, C.c.	Pig	Weight, Gm.	1 C.c. Toxin Subcu-taneously	Result	Amount Injected Intraperi-toneally, C.c.	Pig	Weight, Gm.	1 C.c. Toxin Subcu-taneously	Result	Pig	Weight, Gm.	1 C.c. Toxin Subcu-taneously	Result
1	65	5	689	280	1/15 L+	Discharged	1	A512	240	1/15 L+	Discharged	688	275	1/15 L+	Death, 72 hrs.
2	33	4	A523	280	1/15 L+	Discharged	1	A528	275	1/15 L+	Discharged	281	280	1/15 L+	Death, 72 hrs.
3	44	5	A527	275	1/15 L+	Discharged	1	A531	260	1/15 L+	Discharged	524	270	1/15 L+	Death, 72 hrs.
4	37	5	A166	375	1/15 L+	Discharged	1	A596	205	1/15 L+	Discharged	500	280	1/15 L+	Death, 96 hrs.
	37	5	A191	245	1/15 L+	Discharged									
5	60	7½	534	305	1/10 L+	Discharged	1	521	270	1/10 L+	Discharged	538	295	1/10 L+	Death, 48 hrs.
6	41	6	A497	280	1/15 L+	Discharged	1	A500	195	1/15 L+	Discharged	A499	255	1/15 L+	Death, 48 hrs.
7	32	5½	A166	275	1/15 L+	Death, 7th day	1	A484	250	1/15 L+	Discharged	A317	265	1/15 L+	Death, 48 hrs.
												A596	250	1/15 L+	
8	30	6	A481	300	1/15 L+	Discharged	1	226	235	1/15 L+	Discharged	255	270	1/15 L+	Death, 48 hrs.
	53	7½	A171	215	1/15 L+							235	260	1/15 L+	
	53	6½	A480	235	1/15 L+										

TABLE 7.—*Results of Protection Tests with Transitional Milk and Cord Blood*

	Transitional Milk						Cord Blood					Controls			
Case	Hours Post-partum	Amount Injected Intraperitoneally, C.c.	Pig	Weight, Gm.	1 C.c. Toxin Subcutaneously	Result	Amount Injected Intraperitoneally, C.c.	Pig	Weight, Gm.	1 C.c. Toxin Subcutaneously	Result	Pig	Weight, Gm.	1 C.c. Toxin Subcutaneously	Result
1	60	7	A635	220	1/15 L+	Death, 72 hrs.	1	219	210	1/15 L+	Discharged	A507	230	1/15 L+	Death, 48 hrs.
	60	5	A487	245	1/15 L+							255	290	1/15 L+	
	60	5	225	225	1/15 L+										
2	80	8	A496	275	1/15 L+	Death, 48 hrs.	2	235	195	1/15 L+	Discharged	A429	255	1/15 L+	Death, 48 hrs.
												A498	215	1/15	Death, 24 hrs.
3	72	2	A587	275	1/15 L+	Death, 72 hrs.	1	A635	250	1/15 L+	Discharged	A592	300	1/15 L+	Death, 73 hrs.
	72	2	A634	275	1/15 L+										

1 c.c. of colostrum died; whereas, the one that had received 4 c.c. survived, indicating that in this instance a certain amount of antitoxin was present in the colostrum. In the three remaining cases, 1 c.c. of the serum did not give complete protection, but in all of them death was delayed in the pigs given serum injections, longer than in those that had received colostrum. The concise fact apparent from these twelve cases is that the antitoxin content of the colostrum is less than that found in the cord blood of the same case.

The fact that, in the measurements described in Table 5, a certain amount of protective action was observed when sufficient amounts of colostrum were used encouraged us to continue with series in which we employed the largest amounts of colostrum available, instead of attempting to divide the colostrum into various samples and to make quantitative estimates. The series in Table 6 represents an experiment in which the amounts of colostrum were never less than 4 c.c., and as high as 7.5 c.c. in individual cases.

Results: In this series of eight cases, as presented in Table 6, the cord blood in amounts of 1 c.c. protected with regularity, as did the colostrum of the same cases in quantities ranging from 4 to 7.5 c.c. In one case, only, in which 5.5 c.c. of the colostrum had been injected, the guinea-pig died after seven days. The experiment thus shows definitely that antitoxin may be contained in the colostrum, and, taken together with the results in Table 5, it would seem to indicate that the antitoxin content of the colostrum is regularly less than that of the cord blood. Nevertheless, we realize that the experiment outlined in Table 6 is defective to this extent: we have no means of quantitatively estimating or comparing the antitoxin content of serum and of colostrum, except in Case 7. This defect was unavoidable because, owing to our desire to waste none of the colostrum, we injected the largest available amount into the pig in each case. However, there seems little reason seriously to question the relatively larger antitoxin content of the cord blood.

The methods used in the foregoing experiments with colostrum were applied without change of principle in the following experiments, in which we investigated the antitoxin content of milk and transitional milk. The only difference in these cases was that we used considerably larger quantities of the milk. In the case of the transitional milk, the amounts were similar to those used in the case of colostrum.

The experiments summarized in Tables 7 and 8, then, show that we were able to find no protective, and therefore no antitoxic, properties either in transitional milk, or in milk, in spite of the fact that in a number of cases investigated a certain amount of protective effect had been manifested during the colostrum stage.

Evidence That the Antitoxic Titer of Infants' Serum After the Ingestion of Antitoxin-Containing Colostrum is Not Raised Above That in the Cord Blood.—Blood was obtained from the infants in five of the cases in which the colostrum had given definite evidence of containing antitoxin (Table 6). The children were bled at intervals of from six to ten days after birth, and the serum was collected after clotting. The antitoxin contents of this serum was them determined by the Roemer method and compared in parallel experiments with serum previously obtained from the cord blood of the same case.

Table 8.—*Results of Protection Tests with Milk*

	Milk						Controls			
Cases	Days Post-partum	Amount Injected I. P. C.c.	Pig	Weight	1 C.c. Toxin Subcut.	Result: Death in	Pig	Weight	1 C.c. Toxin Subcut.	Result: Death, Hours
1	12	8	A492	365	1/10 L+	48 hours	535	335	1/10 L+	48
2	10	7	A536	260	1/15 L+	72 hours	A524	270	1/15 L+	72
3	11	10	A496	220	1/15 L+	48 hours	500	280	1/15 L+	96
4	4	6	A495	210	1/15 L+	72 hours	A317	265	1/15 L+	48
5	10	8	A507	345	1/10 L+	72 hours	440	315	1/10 L+	48
							258	230	1/10 L+	
6	4	8	A522	370	1/10 L+	72 hours	A535	335	1/10 L+	48
7	4	8	499	325	1/15 L+	72 hours	281	280	1/15 L+	72
8	4½	6	A166	220	1/15 L+	48 hours	255	220	1/15 L+	48
	4½	6	A440	220	1/15 L+		571	290	1/15 L+	72
9	12	10	A499	220	1/15 L+	5 days	500	280	1/15 L+	96

Table 9.—*Results of Tests of Infants' Serum from Six to Ten Days After Birth*

Case	Toxin Dose in 0.1 C.c.	Serum from Cord Bloods 0.1 C.c.	Infants' Serums 0.1 C.c.	Unit of Antitoxin per C.c. of Cord Blood	Unit of Antitoxin per C.c. of Infant's Blood
1	1/50 L+	—	—		
	1/25 L+	+	+	1/5	1/5
2	1/5 L+	—	—	2 units or more	2 units or more
3	1/25 L+	—	—	2/5 or more	2/5 or more
4*	1/50 L+	—	—		
	1/25 L+	—	+	2/5	1.5
5	1/50 L+	—	—		
	1/25 L+	+	+	1/5	1/5

* Titrations repeated three times.

Result: Table 9 shows that in none of the cases examined did the serum of the infant taken from six to ten days after birth, after ingestion of all the colostrum which the mother could furnish, show any increase of antitoxin content over that of the original cord blood. In Cases 2 and 3, there was too little serum available to complete the titrations. But as far as they could be carried out they showed no difference between the cord blood and the serum of the infant. In one case, in which three separate titrations were made, the titer of the infant's blood was regularly lower than that of the cord blood.

Identical results were obtained in seven other cases, as shown in Table 10. In these cases, the mothers all gave Schick negative reactions, but we had no opportunity to examine the antitoxin content of the colostrum of these women.

CLINICAL INQUIRY INTO THE IMPORTANCE OF COLOSTRUM TO THE NEW-BORN INFANT

As stated in our introduction, the work recorded in this paper was undertaken largely as a result of the investigations of Theobald Smith and his co-workers on calves. His investigations seem to indicate that, in these animals, colostrum was not only important, but could be regarded almost as essential to survival, a majority of the animals that never received colostrum dying during the first week of life of a *Bacillus coli* infection, spoken of as scours. Although it was quite apparent to Theobald Smith that no sweeping application of these observations to conditions prevalent in human beings could be made, it, nevertheless, seemed of considerable importance to investigate this question experimentally.

TABLE 10.—*Results of Tests of Infants' Serum*

Case	Toxin Dose in 0.1 C.c.	Serum from Cord Bloods 0.1 C.c.	Infants' Serums 0.1 C.c.	Unit of Antitoxin per C.c. of Cord Blood	Unit of Antitoxin per C.c. of Infant's Blood
1........................	1/50 L+	—	—		
	1/25 L+	+	+	1/5	1/5
2........................	1/100 L+	—	—		
	1/50 L+	+	+	1/10	1/10
3........................	1/15 L+	—	—		
	1/10 L+	+	+	2/3	2/3
4........................	1/50 L+	—	—		
	1/25 L+	+	+	1/5	1/5
5........................	1/50 L+	—	—		
	1/25 L+	—	+	2/5	1/5
6........................	1/15 L+	—	—		
	1/10 L+	+	+	2/3	2/3
7........................	1/15 L+	—	—		
	1/10 L+	+	+	2/3	2/3

Essential to a proper understanding of the conditions in man was a determination of the relative importance of the transmission of antibodies from mother to infant through the placenta or through colostrum and milk. This was particularly important in view of Smith's conclusion that the value of the colostrum in calves depended largely on the transmission of antibodies. In carrying out these studies, we should have liked to include investigation into the transmission of agglutinins and other antibodies, as well as into these conditions as applied to antitoxins, which, after all, are physically and chemically quite distinct from other protective substances in serum. A lack of suitable material prevented this. We, therefore, believed it best to restrict ourselves to an accurate study of an antibody that could be measured with precision, and for this reason studied the transmission of antitoxin.

Although such studies seemed to us of distinct value, they have little meaning from the purely clinical point of view unless they are combined with an inquiry into the degree to which colostrum actually contributes to the health of the new-born child; for the point of departure of Theobold Smith's investigations was the clinical observation of this essential rôle played by colostrum in the survival of calves.

TABLE 11.—*Clinical Records of New-Born Infants Who Never Obtained Colostrum* *

Case	Days in Hospital	Birth Weight		Weight on Discharge		Feedings	Remarks	Cause of Death of Mother
		Lbs.	Oz.	Lbs.	Oz.			
1	31	4	12	4	7	6:20 formula	Child thin; in need of special care	Hemorrhage
2	120	4	1	10	..	Modified formula	Always did well...........	Eclampsia
3	44	3	15	5	7	Powdered milk	Premature; developed pustules, which cleared on the 15th day	Eclampsia
4	20	6	13	6	14	8:20 formula	Initial loss, 8 oz.; then gained until discharge	Bronchopneumonia
5	45	5	3	6	3	8:20 formula	No fluctuation; child in good condition	?
6	7	2	6	2	4	Modified formula	Birth premature; temperature always subnormal; death on 7th day	?
7	20	6	2	6	8	6:20 formula	Developed abscesses from 10th day on, but all cleared; stools remained normal; temperature normal; gained in weight	Toxemia of pregnancy; hemorrhage
8	78	3	14	6	9	6:20 formula	Premature; developed eye discharge; which cleared up; temperature normal	Toxemia
9	23	8	2	8	4	Powdered milk	Gained 7 oz. from 21st to 23d day	Bronchopneumonia
10	14	5	12	5	2	Modified formula	Initial loss, 14 oz.; then started to gain	Eclampsia
11	6	6	2	6	6	Powdered milk	Practically no initial loss; temperature normal	Eclampsia
12	45	6	10	7	14	Formula alternated with breast milk	Stools green, with curds, gradually becoming normal; after 30 days, developed abscesses on abdomen, which cleared in a week	Eclampsia
13	7	6	2	6	7	Powdered milk	No initial loss.............	Eclampsia; cesarean delivery
14	13	4	12	3	11	Breast milk	Premature; cyanotic; hemorrhagic disease of new-born; received fluids, transfusions; died	Eclampsia during delivery
15	16	7	..	6	13	Modified formula	Initial loss, 10 oz.; then progressively gained 8 oz.	Eclampsia; lived
16	32	5	3	6	0	Modified formula	Premature; temperature normal; stools normal	Eclampsia
17	7	8	9	7	12	Modified formula	Took food well; started to gain	Hemorrhage
18	7	?	?	8	2	Condensed milk, then breast milk	Brought to hospital after delivery because of hemorrhage of mother; put on condensed milk, then to breast after colostrum had been withdrawn	Mother lived

* From the files of Sloane Maternity Hospital, New York Nursery and Child's Hospital and Manhattan Maternity Hospital for the last three years, 1919-1922.

Although it is not easy to obtain such records in human beings, we believed it distinctly worth while to make an extensive search of available records of hospitals accessible to us. By searching the files of the Sloane Hospital for Women, the New York Nursery and Child's Hospital and the Manhattan Maternity Hospital, we succeeded in finding eighteen cases in which the records were sufficiently complete to seem to us to offer valid material for information on this question. We studied the records of the hospitals named over a period of three years, from 1919 to 1922. The evidence in no case was considered sufficiently reliable for our purposes unless the mother had died during delivery, or within the first twenty-four hours after delivery, and unless there was unquestionable evidence in the record that the infant had never been put to the breast. It is not surprising that rigid adherence to such rules resulted in a relatively small yield of available cases. In two cases only were these rules relaxed, and in these the entire clinical course was under our direct control, and we were able to assure ourselves by personal observation that colostrum was never ingested.

In Table 11, we summarize the facts that seem to us essential to a proper appraisal of these eighteen cases.

Results: As far as any conclusion can be drawn from a clinical series as small as the one recorded in Table 11, it would seem that we were justified in assuming that no serious harm attributable to lack of colostrum accrues to the new-born child. The clinical records of these children differ in no way from the average clinical course of colostrum-fed infants. In no case did the records show diarrhea, septic infection, or any of the symptoms of disease analogous to that which seems to occur with such regularity in calves deprived of colostrum. In only Cases 6 and 14 did the children die, on the seventh and thirteenth day after birth, respectively. Both were premature, the first weighing only 2 pounds and 6 ounces (1,077 gm.), a weight which is generally regarded as incompatible with life; the other case was recognized as an unmistakable instance of hemorrhagic disease of the new-born. Three other infants were premature (Cases 3, 8 and 16), and these did well, indicating that even prematurely born children may thrive without the aid of colostrum. It seems of further importance that all of the children in the series were born of mothers who died of severe toxemia, bronchopneumonia or hemorrhage, and in many instances death occurred during labor. These facts, if of any weight at all, are additional evidence in favor of the nonessential nature of the colostrum, since all of these children started under unfavorable conditions.

COMMENT

The studies here reported were undertaken largely because of the possibly important bearing on infant feeding of the work of Theobald

Smith and his collaborators on the essential nature of colostrum feeding in calves. Smith's observations were limited, both in experiment and conclusions, to calves, and no suggestion was made by him that similar conditions might prevail in human beings. Indeed, in our first consultation with him, he suggested probably fundamental anatomic and physiologic differences which should prevent loose generalization in the application of his results to other species. In spite of this fact, his paper was followed by a number of editorial and other articles in the medical press in which such generalizations were made, and in which the observations of Theobald Smith and his pupils were regarded as directly applicable to man. It seemed essential, therefore, that the problem as applied to human beings be made the subject of direct experiment.

In attempting to explain the reason for the protective effect of colostrum in calves, Theobald Smith suggested the possibility that colon bacillus infection, which is etiologically basic to the disease known as scours, might be arrested or prevented by antibodies conveyed to the calves in colostrum. This suggestion was largely based upon the observations of Little and Orcutt, assistants of Theobald Smith, to the effect that the blood of new-born calves did not contain agglutinins against *Bacillus abortus* until after the intake of agglutinin-containing colostrum. Howe, furthermore, showed that the globulin fractions of the proteins which are usually associated with antibodies are lacking in the new-born until after the calves have ingested colostrum, which contains these globulins.

These observations on calves suggested to us that the most direct approach to the problem in human beings lay along two separate lines of investigation: (1) the determination of the manner in which antibodies are conveyed from mother to child, comparing antibody contents of colostrum with those of the blood of the mother, the cord blood and the blood of the infant, after the ingestion of colostrum, and (2) by a clinical study of any reliable records of noncolostrum-fed infants that we could find.

On some phases of this problem, a considerable amount of work has been done in the past. We refer, particularly, to the work of Famulener, published in 1912. Famulener studied the transmission of hemolysins from actively immunized goats to their kids, during the course of pregnancy. The gist of Famulener's studies, which have been mentioned in our introduction, was that these antibodies were transmitted chiefly by the colostrum, but it is worth mentioning that he obtained transmission only in cases in which the mother goat had been immunized to a considerable degree, and possessed a relatively high concentration of hemolytic antibodies.

In view of Theobald Smith's observations, we would have preferred to carry out our work by studying the transmission of agglutinating antibodies, since this would have had more direct bearing on preceding investigations. But, failing, after investigation at a number of large hospitals, to find cases in which agglutinins, either for typhoid or colon bacilli, were present in sufficient concentration in the mother to make the inquiry of value, we finally restricted our study to the transmission of diphtheria antitoxin, since this substance is frequently present in accurately measurable quantities in human beings, and since it lends itself to precise quantitative determination by a variety of methods applicable to conditions such as those investigated by us.

The literature of past investigations into the transmission of antitoxin presents many contradictions. In studying these, it became apparent to us that these contradictions might easily be explained by the fact that various investigators had worked with animals of different species, and a study of the histologic structure of the placentas of the various species employed, as tabulated in the work of Grosser, revealed an astonishing coincidence of placental transmission with relative histologic simplicity of placental structure. Thus, positive placental transmission was generally found in the species grouped as possessing a placenta vera, in which only one cellular layer intervenes between maternal and fetal blood; while in researches in which no placental transmission was revealed, the animals studied generally belonged to species in which the placental structure was considerably more complex.

It is interesting to note, at this point, some of the striking differences in the conditions of mammary secretion in animals, such as cows, with the placenta impermeable, and the new-born calf dependent mainly on the colostrum for the transmission of antibodies; and in man, with the placental structure simpler and more permeable. The cow's udder at the time of parturition is filled with approximately 20 pounds of colostrum, which is immediately and reflexly ingested by the calf shortly after birth to the extent of about two pounds at the first feeding. In human beings, colostrum does not appear for at least twelve hours after birth and is secreted in amounts not greater than 5 c.c. in the first twenty-four hours after birth, and not exceeding 90 c.c. after forty-eight hours; and in this case nursing of the child is not spontaneous but must be stimulated.

CONCLUSIONS

1. A striking difference exists in regard to the passage of antibodies through the placenta in various species of animals, as shown by a review of the literature. In goats and cows, with a placental structure fairly complex, placental transmission of immune substances does not occur, and the colostrum is the main agent for transmitting

immunity from mother to offspring. In rodents and man, with a placental structure relatively simple, placental transmission of immune substances has been demonstrated by many different observers.

2. In accordance with the results of previous workers, we have found that the human placenta is permeable to diphtheria antitoxin.

3. In mothers giving a negative Schick reaction, both the maternal and the cord blood contain at least one-thirtieth unit of diphtheria antitoxin per cubic centimeter, as determined by the Kellogg method. In mothers giving a positive Schick reaction, both the maternal and the cord blood contain less than one-thirtieth unit of diphtheria antitoxin per cubic centimeter, as determined by the Kellogg method.

4. Comparative Schick reactions on mothers and infants show that mothers giving negative Schick reactions give birth to infants giving negative reactions.

5. Infants born of mothers giving Schick positive reactions fail, in a certain percentage of cases, when the cord blood has been shown to be deficient in antitoxin, to give a positive Schick reaction. This depends probably on technical difficulties coincident to intracutaneous injections in new-born infants. A Schick negative reaction in a new-born infant cannot, therefore, with certainty be interpreted as meaning that the infant is immune to diphtheria. Hence, we suggest that, if the susceptibility of very young infants to diphtheria is to be determined, the Schick test can most easily and reliably be performed on the mothers, since the placental transmission of diphtheria antitoxin has been conclusively proved.

6. The concentration of antitoxin in the cord blood corresponds with considerable accuracy to that in the blood of the mothers, there being no measurable loss of antitoxin in passage through the placenta.

7. Human colostrum occasionally contains small amounts of antitoxin, but this amount is always less per volume than that found in the blood serum of the mother or in the cord blood.

8. Transitional milk and milk, in our investigations, never showed the presence of antitoxin.

9. The antitoxin content of the infant's blood in none of our cases showed an increase attributable to colostrum feeding.

10. Careful clinical study of eighteen cases in which there was no possibility of error concerning the ingestion of colostrum revealed no evidence of any possible harm to the infant due to the omission of colostrum.

11. As far as our investigations go, they indicate that colostrum feeding in human beings has no significance whatever comparable to that revealed by the work of Theobald Smith and his co-workers in the feeding of the newborn calf.

A CASE OF CEREBRAL CYST IN AN INFANT *

H. G. JACOBI, M.D.
NEW YORK

Cysts of the brain are of infrequent occurrence, and their detection clinically is extremely difficult. In the majority of cases, the condition is diagnosed only by postmortem examination. The case reported herewith presented several interesting features, briefly: (1) the sudden onset of symptoms simulating an acute infectious process; (2) indefinite signs and symptoms, making an antemortem diagnosis impossible, and (3) the presence of hyperglycemia and glycosuria.

In reviewing the literature, it is of interest to note that Starr,[1] who collected 299 cases of brain tumors in children, found that thirty of these, or nearly 10 per cent., were cysts. The locations were: basal ganglion and lateral ventricle, 1; pons, 1; medulla, 1; base, 1; cerebellum, 9, and centrum ovale, 15. Two of the tumors were multiple. Several interesting cases have been reported, occurring in adults. Anglade [2] reported a case of hydatid cyst of the brain. His patient, a woman, aged 44 years, was afflicted with epileptiform seizures and hemiparesis of the left side, dulling of the intellect, dysarthria and an intention tremor. The cyst was located beneath the posterior horn of the lateral ventricle of the left side and measured about 6 cm. in the long axis and 4 cm. in width. Ross [3] reported a case in a woman, aged 55 years, who had mental symptoms, hemiparesis on the left side, cerebellar ataxia and an intention tremor. Here the cyst was situated in the anterior part of the third ventricle, arising as a simple retention cyst from the connective tissue of the velum interpositum. Lambert,[4] Hoppe,[5] Hunt,[6] and Remsen [7] have reported similar cases.

---

* Received for publication, April 19, 1923.

* From the Jacobi Division for Children, Lenox Hill Hospital, Dr. A. L. Goodman, Director.

[1] Starr, M. A.: Organic and Functional Nervous Diseases, Ed. 4, Philadelphia, Lea & Febiger, 1913.

[2] Anglade, D.: Hydatid Cyst in Brain, J. de méd. de Bordeaux **92**:119-121 (March 10) 1921.

[3] Ross, D. M.: Notes on a Case of Cyst in the Third Ventricle, J. Ment. Sc., London **63**:252-257, 1917.

[4] Lambert, A. V. S.: Cyst of the Interpeduncular Space, Neurological Bull. **2**:53 (Feb.) 1919.

[5] Hoppe, H. H.: A Report of Seven Operations for Brain Tumors and Cysts, J. A. M. A. **36**:302 (Feb. 2) 1901.

[6] Hunt, J. R.: Congenital Cysts of the Fourth Ventricle, Am. J. M. Sc., March, 1904.

[7] Remsen, C. M.: Operative Intervention in Cysts of the Left Cerebral Hemisphere, etc., J. A. M. A. **63**:1649 (Nov. 7) 1914.

REPORT OF CASE

History.—A boy, aged 1 year, admitted, Oct. 28, 1922, with the complaint of vomiting and drowsiness of one day's duration, had a negative personal history except for the fact that, three weeks prior to admission, he had had several attacks of vomiting, extending over a period of two days. These occurred without any regularity or relation to the intake of food, were not projectile and ceased on the next day. The family history revealed that the first child had died at an early age from an unknown cause. The second child was living and well. The father was definitely tuberculous.

The patient had vomited twice on the morning previous to admission, and had appeared drowsy and out of sorts. On the day of admission, he was semicomatose. He had a good bowel movement that morning, and in addition an enema had been given, with good results. The appetite was poor. The infant was extremely restless and its sleep had been interrupted by sharp sudden outcries. Occasionally, convulsive movements were noticed, during which the head was thrown back, the abdomen arched forward and the extremities extended.

Examination.—The infant was in a comatose state, breathing rather heavily. The entire body was completely relaxed and felt cold. The pulse was 82 per minute and irregular both in rate and in force. The temperature was 95.6 F. The respirations were 40. There was a bilateral ptosis present, and both pupils were dilated and failed to respond to light. The corneal reflex, however, was still present, and the eyegrounds were negative. The ears and nose were negative. The tongue was coated and protruded from between the lips, which were dry. The other positive findings were: signs of beginning pulmonary edema; weak and irregular heart sounds; distended bladder; exaggerated knee-jerks and the presence of a Babinski reflex. There was no ankle clonus or Kernig reaction.

Laboratory Findings.—The white blood cells numbered 25,000; polymorphonuclears, 82 per cent.; lymphocytes, 18 per cent. Lumbar puncture showed the spinal fluid to be under normal pressure and clear, with a cell count of 900, of which 78 per cent. were lymphocytes and 22 per cent. polymorphonuclears. Culture of the fluid was sterile. The globulin reaction was markedly positive.

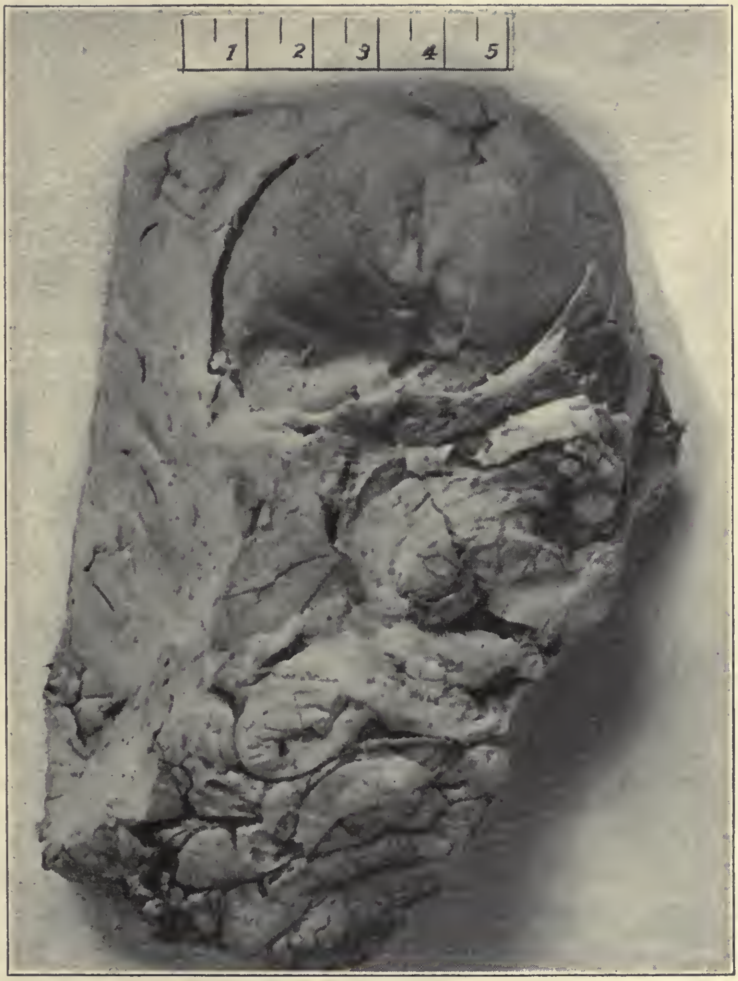
Chemical analysis of the blood showed a creatinin content of 0.7 mg. per hundred cubic centimeters of blood, and a sugar content of 175 mg. The urine, which was straw colored, on admission showed a specific gravity of 1.011. It contained no albumin, but showed a considerable amount of reducing substance. The following day, a second examination revealed albumin and 0.8 per cent. of sugar. The sediment contained several groups of epithelial cells and many bacteria.

Clinical Course.—The patient continued in a comatose state, with the temperature gradually rising until it reached 105 F., the following evening. The pulse became more rapid and irregular. The edema of the lungs became more marked, and death occurred from respiratory failure, about thirty hours after admission.

Necropsy Findings.—Skull: When the calvarium was opened an excessive amount of cerebrospinal fluid escaped. The convolutions were markedly flattened, more so over the right than over the left hemisphere. There was a marked edema involving the pia of the brain. When the lateral ventricles were opened, they were found to be considerably distended. Beneath the posterior horn of the lateral ventricle of the right side, and separated from the ventricle by 0.2 mm. of brain tissue, was a fluctuating cyst, on the surface of which were numerous newly formed blood vessels of fair diameter. The cyst distorted the lenticular nucleus and was not adherent to the brain tissue, from which it could be shelled out. The outer surface of the brain in the posterior convolutions covered the cyst to a thickness of 0.3 cm. The cyst wall was thin. dense and white. It contained 60 c.c. of a creamy yellowish fluid, the chemical analysis of which will be given later. Its cellular content consisted of a large number of lymphocytes, which were undergoing fatty degeneration.

Lungs: Both lungs showed, in their posterior and inferior aspects, a diffuse edema, without areas of consolidation.

The liver, pancreas, gallbladder, suprarenals, bladder, ureters, kidneys, gastro-intestinal tract and spleen were normal. The lymph glands of the mesentery of both the large and the small intestine were enlarged, measuring from 0.04 to 1.2 cm. in diameter, and were pink. There was a secondary paralytic ileus involving the last half of the small and the first half of the large intestine.



Section of right cerebral hemisphere showing cyst, posteriorly situated, with lateral ventricle removed.

Microscopic Examination.—The mesenteric glands showed a partially healed tuberculous process. The cyst wall was composed of dense, laminated connective tissue, richly infiltrated with round cells and having adherent to its inner surface a fair number of polymorphonuclear leukocytes.

The contents of the cyst consisted of a cloudy greenish fluid, colloid in nature, which, on chemical examination, proved to be insoluble in water and acetic acid but was dissolved by dilute potassium hydroxid. The principal constituent was pseudomucin, which yielded a carbohydrate (glucosamin). The specific gravity was 1.029; total nitrogen, 1.3 gm.; total protein (Purdy method), 2.78 gm.; uric acid, 5.5 mg. per hundred cubic centimeters; creatinin, 0.085 mg.; potassium, 0.04 mg.; calcium, 0.0116 mg.; sodium, 0.162 mg.; chlorids as sodium chlorid, 0.360 per cent., and cholesterol, 200 mg. per hundred cubic centimeters. This type of cyst, according to Hammersten,[8] may be considered of the proliferative type, the characteristic constituents of which are metalbumin and paralbumin.

COMMENT

Clinical Data.—This report shows how confusing the clinical picture may be in cerebral conditions of infants, especially when no localizing signs can be elicited. One has to depend usually on objective findings, such as the presence of pathologic reflexes, to be able to arrive at a diagnosis. Even these are often misleading. The presence of a Babinski reflex is without significance at this age.

While a carefully taken history may sometimes lead one to suspect the presence of such a condition, we must remember that various disorders of infancy may set in with fever, vomiting and convulsive seizures.

The presence of hyperglycemia and glycosuria in this case is of interest. It is rather difficult to say whether they may be regarded as features of a terminal condition, or whether pressure of the cyst on the fourth ventricle stimulated the so-called carbohydrate center, simulating the puncture diabetes of Claude Bernard,[9] who found that injury to the floor of the fourth ventricle in dogs and rabbits produced, almost invariably, a discharge of sugar in the urine. This was known as the sugar puncture. The glycosuria was only temporary and never had a fatal ending. It was found, on further investigation, that the puncture produced glycosuria only when the animals had been fed on carbohydrates or were well fed. Starving animals produced little or no sugar.

What the actual cause of death was in this case it would be difficult to state. It seems likely that there occurred a sudden distention of the cyst, with increasing pressure upon the vital centers.

Pathology.—The formation of cysts in the brain has been attributed to a variety of causes. Bruns, while admitting that the etiology of such cysts remains largely in doubt, offers the following classification: (1) those of congenital origin; (2) parasitic; (3) traumatic; (4) those resulting from brain softening, and (5) those without any accountable etiology. Various other classifications have been made, none of which seem to cover the field completely.

---

[8] Hammersten and Hedin: Physiological Chemistry, pp. 624-627, 1915.

[9] Bernard, Claude: Leçons sur la diabète et la glycogénèse animale, Paris, 1877.

With regard to those of congenital origin, Bruns[10] has reported that, in several cases of glioma of the pons, he has also found minute cysts lined by ependyma. These were considered as separations from the primary neural tube. Stroebe likewise found small cysts lined by columnar epithelium, in connection with gliomas of the brain. Thus, abnormalities in the primary neural tube anywhere along its course may be the focus of a morbid proliferation. The dermoid cysts may be similarly regarded as of congenital origin. These are exceedingly rare. Cushing reports but one case in his large experience. Another variety of congenital cyst, described by Heschl and Kundart, is the so-called porencephalic type, in which a defect exists in the cortex extending down to the ventricle. This occurs usually in the region supplied by the middle cerebral artery.

Cysts of parasitic origin are due either to the cysticercus or, more rarely, to the echinococcus. Hunt[6] states that they may be differentiated pathologically from the congenital group thus: 1. In the congenital type, the cyst wall throughout is made up of medullated nerve fibers and glia. 2. The cyst is not intercalated but forms an integral part of the stem. 3. There are remnants of epithelial lining present.

Traumatic cysts around penetrating spicules of bone are at times encountered and may give rise to considerable destruction of brain tissue. Hoppe[11] cites a case in which a cyst the size of a cherry developed in the substance of the left temperosphenoidal lobe as a result of a depressed fracture. The fracture was overlooked because it was covered by the temporal muscle.

Various circulatory disturbances occurring in the brain may give rise secondarily to cyst formations. The blood cysts which result from cerebral or cerebellar apoplexy and those following cerebral softening after embolism may be included in this group.

Inflammatory processes involving the brain substance may be responsible at times for the presence of cysts. It is a well known fact that the power of brain cells to regenerate is limited, and so with the removal of the débris resulting from the breaking down of the brain tissue there develops a defect which may go on to cyst formation.

Localized encysted cerebrospinal fluid has been frequently encountered on the surface of both the cerebellum and the cerebrum. Placzek and Krause describe the condition as resulting from inflammatory changes in the arachnoid, which is thickened and may be united to the dura by adhesions. Fluid collects within the meshes of the arachnoid and is walled off by these adhesions. Such changes may also occur

---

10. Bruns: Geschwulste des Nervensystem, 1908; Neurol. Centralb. 1893, 1896.

11. Hoppe, H. H., in Tice: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc. **9**:632.

secondary to localized meningo-encephalitic attacks with cortical destruction, seen in children, when they usually occur with infantile cerebral palsy as an underlying pathologic condition. This group constitutes the so-called arachnoidal cysts.

We come finally to a group which result from secondary degenerative changes. These occur in the various neoplasms involving the brain, and are sometimes referred to as simple serous cysts, or as cystosarcoma, cystoglioma, etc. Fraenkel reports in great detail a series of eight cases, three cerebral and five cerebellar. Of these, the three cerebral and one of the cerebellar cases were due to degenerative softening of gliomatous origin. In the group of four remaining cerebellar cysts, one was due to softening of a carcinomatous metastasis, one to hemorrhagic softening, one to anemic softening resulting from marked vascular disease and one was without any associated condition.

In exactly which group the case presented in this report belongs, according to the above classification, it is rather difficult to state. By a process of elimination, we would be inclined to list it among the growths of congenital origin. The chemical analysis of its contents establishes its proliferative nature, while the pathologic picture is obscured by secondary inflammatory changes.

MALIGNANT HYPERNEPHROMA IN CHILDREN *

LYNNE A. HOAG, M.D.
ANN ARBOR, MICH.

REPORT OF CASE

History.—December 5, 1921, K. T., a girl, aged 4 years and 3 months was brought to the University Hospital because of convulsions alternating with a semistuporous condition. The father and mother, native-born Americans, without apparent endocrine abnormalities, had always been in good health and had a 7 year old boy, who was free from disease. There was no history of chronic diseases in the family. The patient was normal at birth, weighing 7 pounds (3,175 gm.), and had an uneventful feeding history. Dentition began at 11 months, and had proceeded normally. At 15 months, the child was walking, and at 18 months, she was able to say several words. Until the onset of the convulsions, she was well developed mentally, being able to learn and recite little rhymes at the age of 3½ years. Increase in weight and stature had always been steady, without any noticeably sudden changes. The mother said she had always been a "fuzzy" baby, referring to the prominent lanugal hair which covered the whole body. At about 3 years, the hair on the pubes began to increase in amount, length and pigmentation, but this did not particularly impress the parents, who gave information concerning it only after questioning. She had had chicken-pox, and, at the age of 3 years, had influenza, with a complicating bronchopneumonia, from which recovery was complete in three weeks.

October 20, when 4 years and 2 months old, she was suddenly, without preceding apparent illness, attacked by a practically unilateral convulsion causing rhythmic jerking of the left side of the face, the left arm, hand and leg. It lasted three hours, and she was unconscious during this time. For the next six days, she seemed as well as usual, except for a tendency to fall when walking. November 4, a second attack affected the right side in a similar manner and, although it was of shorter duration and less severe, the child did not recover her usual mentality or physical ability, being unable to walk alone, and acting dull and stupid. Her appetite became ravenous, and she cried constantly for food. The parents noticed an increasing abdominal distention and an increase in the size of the external genitals. A third convulsion occurred, November 22, and this time affected the left side again. From then until admission to the hospital, she had been semistuporous and had not talked much except to ask for food. She had given no evidence of blindness, headache or other pain, and had not vomited. The mother said there had been no cough, fever, diarrhea or urinary abnormalities. The patient had never menstruated.

Examination.—At the time of admission, she appeared acutely ill, lying motionless on her back and not noticing her surroundings unless aroused. The rectal temperature was 99.4 F., pulse 94, respirations 24. She could not stand or sit alone. Development was fair and nutrition excellent (Fig. 1). When disturbed, she asked for food in a monotonous, coarse and rather low-pitched voice. The facial expression was stolid and the eyes were staring. The whole body was covered with prominent lanugal hair; the eyebrows and eyelashes were unusually long; the hair of the scalp was abundant and extended

---

* Received for publication, April 25, 1923.

* From the University of Michigan Hospital, Department of Pediatrics and Infectious Diseases, Dr. D. M. Cowie, director.

well down on the forehead; the upper lip and chin were covered with slightly pigmented hair about 0.5 cm. long; the axillae showed a moderate amount of coarse hair. There was a marked tendency toward perspiring in the palms, on the soles and in the axillae. There was no abnormal pigmentation of the skin. The breasts were normal for a girl of her age. The head appeared large, and the parietal bosses were prominent. The eyes were staring, and vision was apparently present. The pupils were round and equal, and reacted to light. There was a varying and indefinite limitation of extraocular motion to the left. The fundus showed no choking of the disks; a point confirmed by Dr. W. R. Parker. The ears, nose and mouth were normal; the tonsils were not enlarged. The neck was short and stocky; the thyroid gland could not be felt.

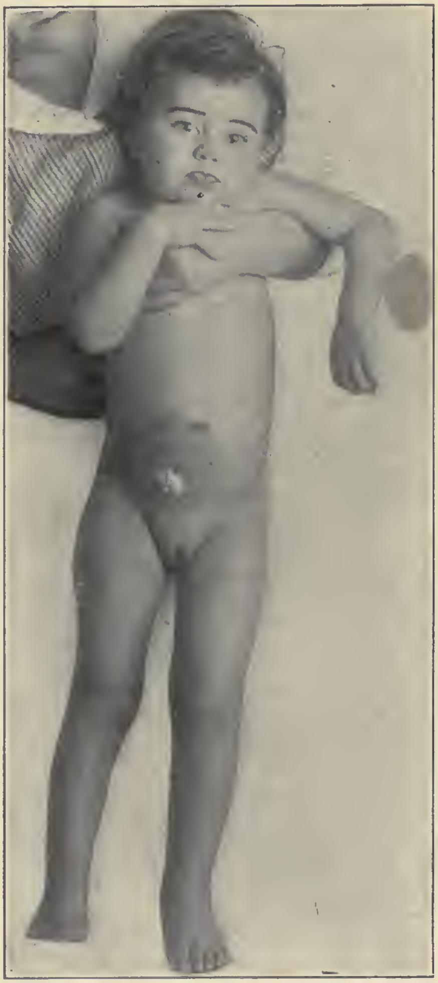


Fig. 1 (Author's Case).—The good nutritional state is evident.

Percussion and auscultation of the chest revealed no pathologic condition of the lungs or heart. The left border of the heart was 7.5 cm. from the mid-sternal line. The abdomen was above the level of the rib margin and was tympanitic, this distention rendering palpation difficult and unsatisfactory. With the aid of deep percussion, an indefinite tumor mass was made out in the right flank just under the liver margin, the latter being 2.5 cm. below the costal margin. Examination of the genitals revealed prominent mons verneris and large labia majora, sparsely covered with pigmented hair averaging 3 cm. in length (Fig. 2). The labia minora were of adult type, and the clitoris was of adult size, measuring 2.2 cm. in length, and having a redundant prepuce. The meatus urinarius and vaginal orifice were in the normal relation. The internal genital organs could not be palpated by rectal examination. The hands were short and broad, with stubby fingers. The left arm was rather rigidly held, and showed little voluntary motion, but not true spasticity, and no paralysis could be made out. The lower extremities were not spastic and showed no atrophy or paralysis. Lack of satisfactory cooperation precluded accurate study of extra-ocular, facial and lingual movements. The biceps, patellar and Achilles reflexes were present, equal and not exaggerated. There was no ankle clonus, and plantar irritation caused plantar flexion of all the toes. Associated movements could not be studied, but there was no tremor or evident asynergia in the voluntary movements. Pin pricks were evidently felt on all skin surfaces, causing complaint and motion. There was no sign of meningeal irritation.

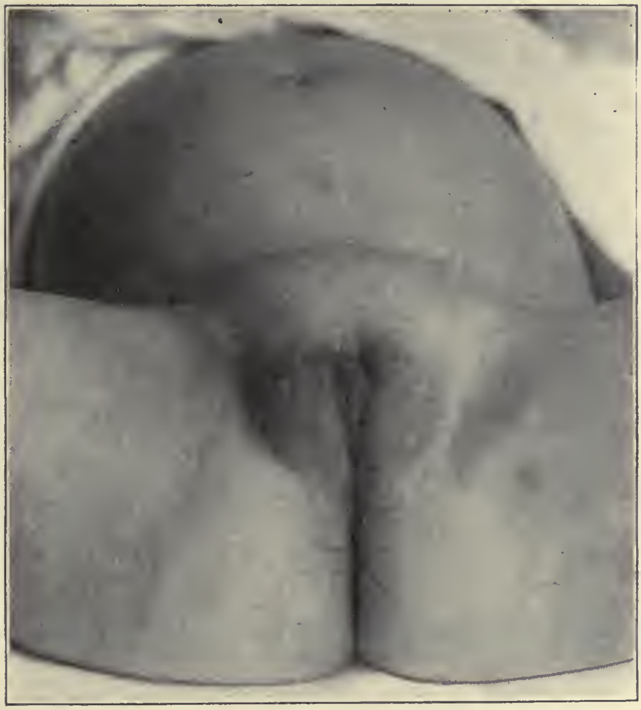


Fig. 2 (Author's Case).—Appearance of genital region, showing prominent mons veneris, adult type of vulva and distribution of hair.

Clinical diagnosis: The probability of an abdominal tumor in a girl of 4 years, showing heterosexual precocity, suggested the clinical diagnosis of malignant hypernephroma.

Laboratory findings: The urine was normal, except for a few leukocytes in the sediment. Examination of the blood revealed: hemoglobin, 88 per cent. (Sahli's test); leukocytes, from 12,000 to 17,000; erythrocytes, from 5,460,000 to 4,880,000; differential count: total mononuclears, 40 per cent., with normal distribution; total polymorphonuclears, 60 per cent., with normal distribution; smear: erythrocytes, normal in size, shape and staining reactions. Blood pressure was: systolic 145-160; diastolic 90-100. The spinal fluid was clear, the pressure moderate; the cells numbered two per cubic millimeter; there was no albumin nor globulin; the Wassermann reaction was negative; Lange colloidal gold and mastic curves were negative; Pirquet skin tuberculin test was negative. Tests of sugar tolerance revealed no glucose in the urine following ingestion, on an empty stomach, of 40 gm. of glucose (2.5 gm. per kilogram of body weight). The blood sugar curve, before ingestion of 1.75 gm. of glucose per kilogram of body weight, dissolved in 120 c.c. of water, taken after fasting fourteen hours, was 0.105 per cent.; at thirty minutes, 0.152; forty-five minutes, 0.150; one hour and twenty minutes, 0.143; two hours and fifteen minutes, 0.141; three hours and ten minutes, 0.100.

Measurements: The standing height (supported) was 96.0 cm.; sitting height, 55.0 cm.; weight, 34.5 pounds (15.7 kg.); pelidisi (Pirquet), 99 per cent.; circumference of head, 50.7 cm.; of chest (at nipple), 52.0.; of abdomen (greatest), 54.2 cm.; crown to umbilicus, 44.0 cm.; umbilicus to sole of foot, 56.5 cm.

Diagnosis: The presumptive evidence of an abdominal tumor in a girl, aged 4 years and three months, showing heterosexual precocity, as evidenced by hypertrophied clitoris, deep voice, and hypertrichosis of distribution characteristic of the male, and brought to the hospital because of convulsions alternating with lethargy, suggested the diagnosis of hypernephroma, with a possibility of intracranial metastasis. To confirm our clinical diagnosis, it was necessary to prove the presence of the suspected tumor mass in the right side of the abdomen. The patient's peritoneal cavity was inflated with carbon dioxid gas introduced through the abdominal wall with an 18-gage needle, and measured by an apparatus similar to that described by Peterson[1] and others. Roentgenograms were taken with the patient on her back, right side and left side, before the carbon dioxid had been appreciably absorbed (inside ten minutes). The right oblique view (patient on left side) showed a mass which at that time was interpreted as being a kidney tumor. Repetition of the procedure five days later yielded a better film, in which it was possible, as reported by Dr. Van Zwaluwenburg, to see above and lateral to the right kidney shadow "another and less clearly defined shadow which appears to be distinct, cleancut in outline, about one-half the size of the kidney. The kidney is evidently displaced downward." The liver shadow was clearly seen overhanging the kidney and tumor shadows. This unusual opacity was interpreted without hesitation as representing a tumor in the region of the right suprarenal.

Two roentgenograms of the skull showed a normal sella turcica, and no evidence of any erosion of cranial bones. The lung roentgen-ray examination gave no evidence of intrathoracic metastasis. Three weeks after admission, the spine failed to show any sign of metastasis by roentgenogram.

Course.—Since the patient had no true localizing neurologic signs in spite of the convulsions, and no evidence of lung metastases, the advisability of attempting to remove the primary tumor was considered. She was seen by Dr. M. M. Peet, who, after the parents urged surgical intervention, consented to perform an exploratory laparotomy. This was delayed for some time by the occurrence of four attacks of convulsions at intervals of several days, each series leaving the patient in such poor general condition that interference was considered inadvisable. The convulsions involved the right and left sides alternately and were not followed by any neurologic localizing signs or any choking of the optic disks. During this delay, the abdominal distention decreased and the tumor mass became progressively more palpable.

---

[1] Peterson, Reuben: Surg., Gynec. & Obst. **33**:154 (Aug.) 1921.

Operation.—Jan. 11, 1922, a large tumor was found behind the peritoneum, covering the upper pole of the downwardly displaced right kidney, and extending upward to the junction of the hepatic veins with the inferior vena cava. It was encapsulated, somewhat lobulated and very friable, most of the center being necrotic and containing extravasated, changed blood. Complete removal was impossible because of the extent of the mass and the patient's poor condition. In spite of blood transfusion she died, four hours after the operation.

Microscopic Examination.—This confirmed the clinical diagnosis of malignant hypernephroma of the right suprarenal cortex.

Necropsy Data (Drs. Warthin and Weller).—The panniculus was 3 cm. thick over the pubes. Section of the breasts showed no glandular tissue. The thymus was very small, showing fibroid atrophy; the corpuscles of Hassal were quite numerous. The heart showed no pathologic changes except a slight right-sided dilatation. The pleura was not adherent. The lungs were studded with numerous nodules, those beneath the pleura varying from 0.5 to 1.5 cm. in diameter. These were sharply circumscribed, soft, yellowish, neoplastic masses, which on section resembled medullary carcinoma, although the general architecture was slightly suggestive of suprarenal cortex (malignant hypernephroma). The lungs were edematous and congested. The thyroid was small, the colloid abundant. The gastro-intestinal viscera and adnexa were normal except for slight hyperplasia of the lymph nodes and Peyer's patches. The left suprarenal was thinner than normal, and on section appeared hypoplastic. The situation of the right suprarenal was occupied by a large neoplastic mass, measuring 10 cm. in greatest length, 6 cm. in width and 5 cm. in thickness, notwithstanding the fact that part of it had been removed surgically. This mass was retroperitoneal but had elevated the peritoneum sufficiently to cause its attachment to the under surface of the liver. The kidney had been pushed downward and was uninvolved in the new growth. On macroscopic section, normal suprarenal tissue was not found. The mass was friable and necrotic in most places, but the firmer portions were light yellow, with a fatty appearance. Microscopically, some areas resembled a suprarenal cortex. The atypical portions more closely resembled a medullary carcinoma, but many of the cells contained lipoids. Some areas showed a marked perivascular arrangement of the cells, more like an angiosarcoma. The kidneys showed cloudy swelling and acute congestion. The vaginal orifice admitted the finger with slight difficulty; the vaginal canal measured 6 cm. in length. The uterus was undeveloped, measuring 3 cm. from fundus to external cervical os. The ovaries were free, 2.0 by 0.5 cm., and showed on section an unusual number of large cystic follicles, but no evidence of menstruation.

Examination of Brain (Dr. A. M. Barrett of the Department of Psychiatry).—The brain had been hardened in 10 per cent. formaldehyd for nine days. It had a length of 16.2 cm. and a breadth of 12.8 cm. In volume, it gave the impression of being larger than usual for a child of this age. The pia mater was clear, with slight congestion of the larger veins. The convolutions of the convexity were normally formed but had not reached full development. In a few places, there were small areas in which the surface of the convolutions appeared softened.

The base of the brain showed erosions of the tip of the temporal lobe from mechanical injuries during its removal. The basilar artery was partly filled with blood clot. At a point about 1 cm. from its bifurcation, there was a small patch of thickening of the artery wall.

Vertical sections of the brain showed no gross abnormalities aside from the small areas of superficial softening. In these, the cortex appeared macerated and separated easily from the underlying white substance.

The pineal gland was somewhat flattened, and measured 7 mm. in width and 5 mm. anteroposteriorly.

Histologic examination revealed a number of pathologic alterations. The pia mater of the convexity was not thickened, and there was no infiltration. In a number of places, notably near the areas of softening, a number of arteries showed marked arteriosclerotic changes. These varied from slight thickening of the intimal layer to an extreme narrowing of the lumen, with an hypertrophy of the intima. The elastic coat was not abnormal. In one vessel, presenting slight thickening of the intima, there were fragments of this layer separated from the underlying coats and extending into a tangled mass of fibers filling the lumen of the vessel.

Sections through the areas of softening showed small patches in which the parenchyma had disappeared, leaving a defect filled with strands and islands of swollen vessels with scattered epithelial cells. Bordering this was an area in which the continuity of the tissue had not been broken but showed dense infiltration with epithelioid cells, marked reduction of the number of nerve cells and a great number of large progressive forms of neuroglia cells. The blood vessels in this area showed swelling of their walls and early proliferative changes. For some distance away from this more markedly altered area, the region showed loss of nerve cells, marked glia hypertrophy, and slighter changes in the blood vessels. These changes involved only the nerve cell layers of the cortex. In their type, they were characteristic of the reaction that occurs from occlusions and arteriosclerosis of the vessels of the pia mater.

The pituitary gland showed normal relations between the glandular and nervous portions, the stalk, and the connective tissue of the capsule in this region. There was a dense accumulation of cells. These lay in clumps and infiltrated the connective tissue for some distance. They were chiefly large mononuclear forms with a large amount of cytoplasm. In most of these, the cytoplasm was compact and homogenous; in others, highly vacuolated. There were also, in places, a considerable number of lymphocyte-like nuclei lying in patches along the stalk.

Diagnosis: Arteriosclerosis of the pial vessels; multiple superficial cortical softenings and pathologic cellular accumulations in the region of the stalk of the pituitary gland were diagnosed.

THE LITERATURE

Precocious sexual development has always attracted much attention, especially when occurring in very young children. The literature contains numerous references to such cases, many of them without evident pathologic basis. The manifestations of precocity are variable. Both the secondary and primary sex characteristics may be involved, resulting in true pubertas praecox, with spermatogenesis and its accompanying manifestations in the male, and with ovulation and menstruation in the female. The term should be carefully restricted to those cases showing the physiologic processes necessary for propogation, and not loosely applied to some of the secondary changes to be noted later. These secondary sex characteristics may be the only ones prematurely developed, and may be either homosexual, the accentuated characteristics being the ones normally found in the sex affected, or heterosexual, showing certain changes considered typical of the opposite sex. Krabbe[2] has recently applied the term virilism to the following syndrome of male characteristics appearing in the female, regardless of the age: hypertrichosis, including face, hypertrophy of the clitoris and deepening of the voice. This syndrome fits the majority of reported cases of suprarenal cortex tumors, and is heterosexual prococity but not true pubertas praecox. It is sometimes accompanied by premature body growth either in the form of (*a*) fat deposits, (*b*) hypertrophied musculature (herculean type) or (*c*) skeletal overgrowth resulting in gigantism.[3] Pelizzi has suggested for this combination the term macrogenitosomia praecox.

---

[2] Krabbe, K. H.: New York M. J. **114**:4 (July 6) 1921.

The etiology of the numerous cases of abnormal sex and body development in children has been definitely determined in only a small proportion of recorded cases. For a general survey of this interesting field two recent articles, Leiner[4] and Tierney[5] furnish a large bibliography. According to Guthrie and Emery,[6] atavistic tendency to early maturity, or hastened old age (progeria) may account for some of the cases in which there are no pathologic findings. Although the thyroid gland is intimately related to body and sex growth, as evidenced by changes in it associated with puberty, menstruation and pregnancy, and changes in the body and genitals associated with congenital or acquired hypothyroidism or athyroidism, it is true that precocious puberty does not occur with tumors of this gland. Linser[3] quotes Fritsche and Klebs as implicating the thymus in growth disturbances. Frohlich's syndrome furnishes a good example of the influence of the pituitary on the somatic and genital systems, and acromegaly is an expression of its effect on somatic growth; but here again true early puberty is not intimately associated with tumors, although retardation of sex development may accompany decreased function of the gland. Occasionally, tumors of the pineal body produce sexual and other forms of physical precocity. Of the seventy or more reported pineal tumors, about twenty-four have been in children (McCord[7]), and only about four were in females.[8] In 1912, Glynn[9] was able to find only five cases proved by necropsy, and associated with sexual precocity. These were all in boys. It is thus readily seen that much confusion exists concerning the actual number of cases of pineal tumors in children causing sex and somatic changes, and the proportion of males and females, although it is clear that the condition predominates in males.

Pathologic changes in the gonads (testis and ovary) are probably the commonest cause of true precocious puberty in the cases showing lesions at necropsy. Tumors of these organs usually cause homosexual prematurity, and surgical removal has been known to result in amelioration of the condition or even complete restoration to normal. The relation of the suprarenal cortex to somatic prematurity was first emphasized by Linser,[3] who collected a few cases showing gigantism, as he called it, associated with tumors of the suprarenals. In 1905, Bulloch and Sequeira [10] collected, and presented in a masterly way, the previously accumulated evidence pointing to the effect exerted on the genital system by the suprarenal glands. They discussed twelve cases of malignant conditions of the suprarenal cortex in children, citing in addition five necropsies which showed hypergenitalism to be associated with simple hypertrophy of the suprarenal cortex, and another series of cases of underdeveloped genitals in which the cortex was hypoplastic or aplastic. It is also interesting to note that they mentioned thirteen cases of primary suprarenal tumors in young children unassociated with any precocious sexual development. Carter [11] has recently emphasized the fact that tumors of the suprarenal medulla do not cause sexual prematurity, but usually evidence themselves first by metastases and the resulting local symptoms. Hypernephroma of adults with lack of sex changes can be explained by the relative stability of the generative system during adult life. In 1911, Glynn [9] collected five more cases of suprarenal cortex tumors, and these, together with the four reported since that time, make a total of twenty-one cases of this condition in children, as verified by operation or necropsy. A brief summary of these cases will help us to formulate a more inclusive clinical picture.

---

[3] Linser, P.: Beitr. z. klin. Chir. **37**:282, 1903.

[4] Leiner, J. H.: Endocrinology **4**:369 (July-Sept.) 1920.

[5] Tierney, J. L.: Med. Clinics N. America **6**:31 (July) 1922.

[6] Guthrie, L., and Emery, W. d'E.: Tr. Clin. Soc. London **40**:175, 1907.

[7] McCord, C. P.: Tr. Am. Gynec. Soc., 1917; Surg., Gynec. & Obst. **25**:250 (Sept.) 1917; The Pineal Gland in Relation to Somatic, Sexual and Mental Development, J. A. M. A. **63**:232 (July 18) 1914; Interstate M. J. **22**:354, 1915.

[8] Baar, H.: Ztschr. f. Kinderh. **27**:141, 1920.

[9] Glynn, E. E.: Quart. J. Med. **5**:157, 1911-1912.

William Cooke [12] (1756): A girl, aged 7 years, enormously fat with a large skeleton, and having copious hair on the face and genitals, died in convulsions. Necropsy revealed internal hydrocephalus and a large tumor extending from the upper pole of one kidney to the upper pole of the other. Neither suprarenal was found. There was no microscopic report.

Bevern and Romhild [13] (1802): A girl, aged 3½ years, fat, and "looking like a woman of 20," had abundant hair on the face and pubes. Necropsy revealed a large tumor in the left abdominal cavity. The exact attachments were not mentioned, nor were the suprarenals mentioned. The case was apparently typical clinically, but pathologic proof was insufficient.

Tilesius [14] (1803): A girl, aged 4 years, with very adipose body and large (fat?) mammae, had well developed pubic hair. Necropsy revealed a tumor the size of a goose egg in the left suprarenal, and metastases to the liver.

---

[10] Bulloch, W., and Sequeira, J. H.: Tr. Path. Soc. London **56**:189, 1905.

[11] Carter, W. E.: Medullary Malignancies of Suprarenal Gland with Report of Cases, Am. J. Dis. Child., **22**:244 (Sept.) 1921.

[12] Cooke, William: Phil. Tr. Roy. Soc. London, 1756. This could not be verified; quoted from Linser (Footnote 3), and Bulloch and Sequeira (Footnote 10), who could not verify it.

[13] Bevern and Romhild: J. d. prakt. Arznk. u. Wundarznk. **14,** Part 3, p. 141.

[14] Tilesius: Quoted by Linser (Footnote 3).

Pitman[15] (1865) and Ogle[16] (1865): A girl, aged 3 years, normal at birth, had presented symptoms for eight months. At 3 years, she was stout, 34½ inches (86 cm.) tall, and weighed 44 pounds (20 kg.). She had a sullen expression, a rude and savage disposition, a rough voice and a voracious appetite. The skin was "gipsy color." There was a general hypertrichosis, with heavy eyebrows, moustache and prominent pubic hair. The genitals were "precociously developed." A tumor was palpable in the left side of the abdomen. Necropsy revealed a tumor of the left suprarenal, weighing 2⅛ pounds (nearly 1 kg.), with metastases to the liver and lungs. The other organs including the uterus and ovaries were normal. The tumor was a "large mass of encephaloid cancerous growth."

Colcott-Fox[17] (1885): A girl, aged 2 years, normal at birth, but "enormous" at 10 months, had a ravenous appetite, dull intellect and dusky pallor of the skin. The vulva, labia and clitoris were precociously developed and the pubic and body hair was prominent. There was a tumor in the left side of the abdomen. At necropsy, this growth was found to replace the left suprarenal. Its weight was 1½ pounds (about 0.7 kg.). The uterus and ovaries were large. There were metastases to the lungs. The tumor was a giant-cell sarcoma.

Dickinson:[18] A girl, aged 3 years, of dull intellect, and having "gypsy" colored skin, a harsh voice and ravenous appetite, had had hair on the pubes since 1 year of age. The condition of the genitals was not recorded. Necropsy revealed a tumor of the suprarenal (side not given), with metastasis to the liver. The growth was "encephaloid."

Orth[19] (1893): A girl, aged 4½ years, normal at birth, had had symptoms since the age of 1 year. The clitoris became like a small penis, and the other external genital organs were precociously developed. There was hair on the pubes, and the face was bearded, requiring shaving for the last six months. A tumor had been palpable in the right side of the abdomen for two and one half years. At necropsy, the growth was found to replace the right suprarenal. There were metastases to the liver and lungs. The tumor was a carcinoma (hypernephroma?).

Dobbertin[20] (1900): A girl, aged 14 months, born with a tumor in the abdomen, had hair on the labia majora, body, cheeks and chest. The genitals were not mentioned. Somatic development was normal. At operation, the tumor, which replaced the left suprarenal, and left kidney were removed. At necropsy, metastases behind the manubrium sterni were revealed. The tumor was a "congenital carcinoma."

Miller[21] (1903): A girl, aged 2 years, normal at birth, had presented symptoms since 1½ years: abdominal swelling and hypertrophy of the labia majora and minora, with sparse hair on the former. The clitoris was enormously enlarged, 1 inch (2.5 cm.) long, with definitely retractable prepuce. Operation revealed a vascular tumor of the right suprarenal. Removal was not attempted. The patient survived exploration, and passed through an attack of measles and bronchopneumonia, dying eleven months later. The history of the intervening period and necropsy findings were reported by White and Nisbet.[22] The child resembled a "little old woman," with thick neck, prominent eyes and dark skin. Necropsy revealed a large tumor of the right suprarenal. The clitoris was 4 cm. long, with a definite prepuce. The pubic hair was abundant. There were metastases to the liver, mesenteric nodes and the right lung. The tumor was a hypernephroma.

---

[15] Pitman: Lancet **1**:175, 1865.

[16] Ogle, J. W.: Tr. Path. Soc. London **16**:250, 1865; Med. Times & Gaz. **1**:532, 1865.

[17] Colcott-Fox, T.: Tr. Path. Soc. London **36**:460, 1885.

[18] Dickinson, W. H.: Quoted by Colcott-Fox (Footnote 17).

[19] Orth, Johannes: Arb. a. d. path. Institut. in Göttingen, Berlin, Virchow, 1893, p. 75.

[20] Dobbertin: Beitr. z. path. Anat. u. z. allg. Path. **28**:42, 1900.

[21] Miller, D. J. M.: Arch. Pediat. **20**:932, 1903.

[22] White, C. J., and Nisbet, V.: Arch. Pediat. **21**:943, 1904.

Linser[3] (1903): A boy, aged 5 years and 7 months, normal at birth, but presenting symptoms for the last 15 months, resembled a youth of from 16 to 18 years. He was 138 cm. tall, weighed 39 kg., and had twenty-eight teeth. All eight carpal ossification centers were present. There had been hair on the mons veneris for one year. The penis was from 8 to 9 cm. long (from 12 to 14 cm. in erection); the testes were the size of pigeon's eggs. A large tumor was palpable in the left kidney region. At operation, no attempt was made to remove the mass. Necropsy revealed a large left suprarenal tumor, with rupture into the vena cava, and metastases to the lungs. The testes showed no spermatogenesis. The thyroid, hypophysis and pineal glands were normal. The thymus was not found. The tumor was a hypernephroma.

Bulloch and Sequeira[10] (1905): A girl, aged 11 years, normal at birth, was intellectually dull; of brunette complexion; had a large face, and "looked like a stout little woman of about 40 years." The height was 4½ feet (135 cm.), the weight, 87 pounds (39.5 kg.). There was hair on the chin, lips and pubes and in the axillae. The breasts were large, resembling those of a sexually mature woman. The patient had menstruated during the last fifteen months (since the age of 10 years). There was a tumor in the left side of the abdomen, which necropsy revealed replacing the left suprarenal. The growth weighed 3 pounds and 1 ounce (1.6 kg.). The thyroid and parathyroid were hypertrophied. The uterus showed enlargement of the cervix. The ovaries were fairly large. The corpora lutea were found. There were metastases to the liver and lungs. The tumor was a carcinomatous hypernephroma.

Ritchie[23] (1905): A girl, aged 4 years, who had abundant pubic hair, had been considered an hermaphrodite, but Prof. Arthur Thompson said that the genitals were normal except for size. In this respect, they resembled those of a developing woman. Menstruation had not occurred. Death followed an osteotomy. Necropsy revealed an unsuspected tumor of the suprarenal (side not given). The growth was "sarcomatous."

Adams[24] (1905): A boy, aged 14 years and 4 months, normal at birth, but presenting symptoms since the age of 10 years, was a "sturdy little man," of great muscular strength. He had had a beard for the last two years; "puberty set in at the age of 10." A tumor was palpable on the left side of the abdomen. Exploratory laparotomy revealed an inoperable tumor in the region of the left kidney. The patient died seventeen months later. Partial necropsy revealed a tumor, weighing 8½ pounds (3.8 kg.), replacing the left suprarenal, encapsulated, and the kidney uninvolved. The liver was enormously enlarged, weighing 15½ pounds (7 kg.), and infiltrated with yellowish tumor masses. The spleen showed metastases. The right suprarenal was normal. The tumor was a malignant hypernephroma (perithelioma).

Walker (verbatim report by Richards,[25] 1905): A girl, aged 8½ years, whose symptoms began at 5 years, became very stout, and developed excess hair on the pubes, face and chin, with silky beard and whiskers. The external genitals were not unduly developed. A tumor was palpable in the left hypochondrium. The abdomen was tapped for ascites. Partial necropsy revealed: left kidney size of coconut, consisting entirely of new growth; right kidney about one-half this size, destroyed by growth; metastases to liver. The suprarenals were not definitely mentioned. The tumors were not sectioned. The case was clinically typical, but the condition was not definitely proved pathologically.

Guthrie and Emery[26] (1907): A boy, aged 4 years and 9 months, normal at birth, had presented symptoms for two years. He gradually became very stout, like a "burly brewer's drayman." The height was 36 inches (90 cm.); weight, 43½ pounds (about 20 kg.). There was flabby fat on the shoulders, trunk, arms, abdomen and breasts. The eyebrows were bushy, and there was coarse hair on the pubes. The genitals were "not unduly developed." Convulsions occurred three months previous to admission to hospital. The patient died of acute tuberculosis. No abdominal tumor was palpable. At necropsy, in addition to disseminated miliary tubercles, a tumor the size of a large walnut, replacing the left suprarenal, was revealed. The right suprarenal was not found. The thymus, thyroid, hypophysis, epiphysis and testes were normal. The latter did not show spermatogenesis. There were no metastases. The tumor was a malignant hypernephroma, carcinomatous and very complex.

---

[23] Ritchie: Quoted by Bulloch and Sequiera (Footnote 10).

[24] Adams, C. E.: Tr. Path. Soc. London **56**:208, 1905.

[25] Richards, Owen: Guy's Hosp. Rep. **59**:217, 1905.

[26] Guthrie, Leonard, and Emery, W. d'E.: Tr. Clin. Soc. London **40**:175, 1907.

Dunn and Glynn[9] (1912): A girl, aged 5 years, whose symptoms began at 3 years, had precocious body development, was "unusually tall," fat and flabby. The hair was profuse on the scalp, upper lip, pubes and back. There was no hypertrophy of the clitoris or mammae. Menstruation had not occurred. Six weeks before death, a tumor was palpable in the right side of the abdomen. Convulsions occurred during the latter part of the illness. Necropsy revealed a tumor, weighing 2¾ pounds (1.25 kg.), 7½ by 5 by 4 inches (3 by 2 by 1.6 cm.), replacing the right suprarenal. It was encapsulated, free from the kidney, and showed a structural arrangement similar to that of the cortex. The areas of Langerhans were prominent. There was exhaustion of colloid in the thyroid. The pituitary and left suprarenal were normal. There were no metastases. The tumor was a malignant suprarenal hypernephroma.

French[27] (1912): A girl, aged 7 years, developed pubic hair at 18 months, and the external genitals became hypertrophied. A large tumor was palpable in the left upper section of the abdomen. A diagnosis of suprarenal tumor was made. At operation, the tumor and the left kidney were removed. Necropsy revealed metastases to the lungs. The tumor was a perithelioma (hypernephroma).

Jump, Beates and Babcock[28] (1914): A girl, aged 7 years, one of twins, normal at birth, at 1 year began to show phenomenal body development and physical strength. At 7 years, she was 53 inches (132.5 cm.) tall, weighed 90 pounds (41 kg.), and had a deep voice, the larynx being like that of a man. The child was well developed mentally. There was hair on the pubes, legs, trunk and chin (distinct beard), and in the axillae. The skin perspired freely. The labia were large. The clitoris was 2.5 cm. long, and grooved on the under surface. The breasts were relatively undeveloped. Menstruation had not occurred. A tumor was palpable in the right side of the abdomen. A diagnosis of tumor of the right suprarenal cortex was made. Removal was attempted, but was unsuccessful, death ensuing in three hours. Partial necropsy revealed that the growth involved the right kidney, without demarcation. The left suprarenal was normal. The uterus and ovaries were infantile. There was no evidence of metastasis in the abdomen. The tumor was a hypernephroma.

Van den Bergh[29] (1915): A girl, aged 3 years, showed "premature development of secondary sexual characteristics" and of the external genitals, without menstruation. At operation, a tumor was removed from the region of the left suprarenal. The growth, which weighed 2 kg., was a carcinomatous hypernephroma.

Schiff[30] (1918): A girl, aged 2 years, had presented symptoms for two and one half months: a ravenous appetite, heavy voice and adiposity. The weight was 11.6 kg., height, 74 cm. The pubic hair was 3 cm. long, and there was a moderate beard. The breasts were normal, and no unusual development of the genitals was noted. There was a palpable tumor in the right side of the abdomen. A diagnosis of hypernephroma was made. An exploratory operation was followed by death. Necropsy revealed a tumor, 16 by 11 by 6 cm., replacing the right suprarenal, separate from the kidney. The thymus, left suprarenal, uterus and ovaries were normally developed. The hypophysis and epiphysis were slightly enlarged, the former showing an increase of eosinophils. The acini of the thyroid were small; the colloid was scanty. Metastasis was not noted. The growth was a hypernephroma.

---

[27] French, Herbert: Cited by Glynn (Footnote 9); Index of Differential Diagnosis, Ed. 2, New York, William Wood & Co., 1917, p. 164.

[28] Jump, H. D.; Beates, H., Jr., and Babcock, W. W.: Am. J. M. Sc. **147**:568, 1914.

[29] Van den Bergh: Nederlandsch. Tijdschr. v. Geneesk., 1915, p. 2217.

[30] Schiff, E.: Jahrb. f. Kinderh. **87**:519, 1918.

Ambrozic and Baar[31] (1920): A girl, aged 3 years, whose symptoms began at 1 year, had a mannish voice, looked like a child of 6 years, and was intellectually advanced. The height was 105 cm., weight 18.3 kg. The musculature was well developed, and there were eight centers of ossification in the wrist. The labia were large and lipomatous; the clitoris was like a little finger, and grooved on the under surface; the breasts were undeveloped. The hair was heavy on the pubes, labia majora and around the arms and scanty in the axillae. A tumor was palpable in the left side of the abdomen. A diagnosis of malignant suprarenal tumor was made. At operation, the left kidney and the tumor were removed. Death ensued the same night. At necropsy, the internal generative organs were normal, except for a proportionately large cervix uteri and vagina. There was a cyst in the region of the pineal gland, but the latter was free. Other organs of internal secretion were normal. There were metastases to the lungs and the right temporo-occipital lobe of the brain. The tumor, which was encapsulated, septate and gray-red, was a malignant epithelial growth, with a structure resembling in places that of the zona fasciculata (hypernephroma).

COMMENT

Of the twenty-two cases of malignant hypernephroma verified by operation or necropsy, nineteen occurred in females and only three in males. In some of the reports, the data are incomplete and make accurate comparative study unreliable. A tumor was clinically demonstrable in the majority of cases, and there seemed to be no preference for either side. With apparently but one exception, the patients were normal at birth, but most of them presented symptoms within the first four or five years of life. The effect on somatic development was not uniform; two males showing marked prematurity in body strength, accompanied by precocious homosexual genital development, the other boy showing large fat deposits, flabby musculature and no undue enlargement of genitals. The females showed a much smaller percentage of somatic changes. Only one had menstruated, and she was 10 years old at the time. The great majority of the girls showed heterosexual precocity: hair on face, deep voice, overdevelopment of the clitoris and lack of development of breasts. The boys invariably showed accentuation of male characteristics. A few showed distinct pigmentation of the skin. Several had ravenous appetites. In spite of the fact that intracranial metastasis was demonstrated at only one necropsy, four patients are mentioned as having had severe convulsions. In nine cases, exploratory laparotomies were performed. The viscera showing metastases most fre-

---

31. Ambrozic and Baar: Ztschr. f. Kinderh. **27**:135, 1920.

quently were the lungs and liver, no author mentioning bone metastases. The other glands of internal secretion did not show any striking or constant changes. The confusing variety of pathologic nomenclature applied to the neoplasms was undoubtedly due to the fact that the microscopic appearance of these masses varied not only in different cases but also in separate portions of the same tumor. The term malignant hypernephroma seems to be most commonly used now, rather than one based primarily on morphology.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the etiology of precocious sexual development involves a consideration of the gonad (testis or ovary), pineal and suprarenal glands especially. Homosexual precocity in the male can be caused by tumors in any of the three, the order of frequency being as named above. Homosexual precocity in the female implicates the ovary in the majority of cases. Heterosexual precocity in a female child is most suggestive of a malignant condition of the suprarenal cortex or hyperplasia.

Pineal tumors have been predominant in males, but the number verified by necropsy is small. According to Marburg, these cases show three groups of symptoms: (1) sexual and somatic abnormalities from the specific effect of the pineal tumor; (2) choked disks, headache, drowsiness and vomiting, from increased intracranial pressure, and (3) focal neurologic signs, as cerebellar ataxia, nystagmus, general paralysis of the cranial nerves (especially the eye innervation group), from local pressure or extension. The neurologic changes are usually coincident with the genital abnormalities, thus helping to differentiate gonad or suprarenal tumors, which may give rise to intracranial metastasis late in their course. Even after an abdominal tumor is demonstrable, it becomes necessary to distinguish between ovarian and suprarenal tumors, which is usually possible clinically. When an abdominal tumor is merely suspected, it is hoped that roentgengrams following inflation of the peritoneal cavity with carbon dioxid will greatly assist in an early and accurate localization.

KRABBE'S HYPOTHESIS

It is well known that, in elasmobranchs, the suprarenal cortex and medulla are separate and have different anatomic structures. In higher vertebrates, including man, this separation is still indicated by the embryologic derivation of the two portions of the united gland, the cortex coming from the genital ridge in close association with the gonad; whereas, the medulla is developed from tissue closely associated with the sympathetic nervous system. This belief in a relation between the gonads and the suprarenal cortex is accentuated by the facts that suprarenals of rabbits are hypertrophied during the breeding season (Stilling); frogs show seasonal variation in the size of their suprarenals, and castration in animals often causes enlargement of the adrenal cortex. Kohn[32] suggests that the origin of the ovary is hermaphroditic, the cortex being the differentiated female portion, but the medulla having sex-cords and interstitial cells resembling in many ways those in the testis, and coming directly from the original undifferentiated genital ridge close to the suprarenal cortex. Normally, these essentially male elements of the ovary remain rudimentary, but Krabbe[2] suggests that occasionally these cells may become incorporated in the neighboring suprarenal cortex and run wild, giving rise to neoplasms, the cells of which are not derived from the suprarenal but from essentially male genital ridge tissue, and therefore give rise to an internal secretion which causes development of male sexual characteristics.

These details are presented in the hope that early recognition of the importance of these subtle early sex changes, together with the rapid improvements being made in the demonstration of abdominal tumors, may make it possible to diagnose such cases early enough to allow successful surgical intervention. This possibility is rendered all the more probable when we remember that metastases from suprarenal cortex tumors are usually late, and that the opposite gland is almost uniformly normal according to our present anatomic and histologic standards.

---

32. Kohn, A.: Arch. f. Entweklngsmechn. d. Organ., 1920, p. 47.

STUDIES OF TETANY

I. THE EFFECT OF CALCIUM CHLORID INGESTION ON THE ACID-BASE METABOLISM OF INFANTS *

J. L. GAMBLE, M.D.
BOSTON

G. S. ROSS, M.D.
Cooper Traveling Fellow, McGill University
MONTREAL
AND

F. F. TISDALL, M.D.
TORONTO

It has for sometime been a matter of observation in this clinic, and no doubt elsewhere, that infants receiving calcium chlorid for relief of the symptoms of tetany will occasionally develop hyperpnea. In these instances a marked lowering of the plasma bicarbonate may be demonstrated.

It is possible to explain an acid effect from the ingestion of calcium chlorid by assuming a more complete absorption of the chlorid ion (Cl^-) than of the calcium ion (Ca^{++}) from the gastro-intestinal tract. The probability that a large part of the calcium will form insoluble phosphates and soaps, and, in consequence, escape absorption affords ground for this surmise. If this is the case the uncovered chlorid ion must be provided before absorption with other base derived from the carbonates and dibasic phosphates of the food. The effect on acid-base metabolism of an excess of the chlorid ion over the calcium ion absorbed should be the same as would be produced by placing in the food an equivalent amount of hydrochloric acid, except to such extent as the calcium ion released from the chlorid ion interferes with the absorption of other inorganic acids and thereby offsets the increased absorption of the chlorid ion. The only other accessible inorganic acid in the food is phosphoric. A lowering of absorption of this acid by the calcium ion from ingested calcium chlorid will doubtless, to some extent, occur, owing to an increased formation of insoluble phosphates. Since, however, much of the calcium from ingested calcium chlorid may reasonably be assumed to be carried into the stools by organic acid products of digestion, a large part of an excess of the chlorid ion over the calcium ion absorbed would not be compensated for; interference with the absorption of these organic acids being of no moment from the point of view of acid-base equilibriums within the body.

The efficacy of calcium chlorid administration in relieving the symptoms of tetany being well established, definite information regarding

---

* Received for publication, March 21, 1923.

* From the Department of Pediatrics, Johns Hopkins University, Baltimore.

the manner and extent of its acid effect is desirable. The experiments to be described in this paper were undertaken with the purpose of obtaining data on this point.

PLAN OF STUDY

The plan of study consisted in obtaining certain data from analyses of stools, urine and blood serum during a fore period, and then repeating the measurements during a period in which calcium chlorid was administered. The same diet, a usual one, was continued throughout. The data obtained from the fore period were used as a basis by means of which alterations in acid-base values during the calcium chlorid period could be noted and approximately measured. Two infants were studied in this way; Infant W., 5 months old, weighing 5.9 kilograms, regarded for the purposes of this study as a normal infant, and Infant H., 4 months old, weighing 4.3 kilograms and presenting, before calcium chlorid was given, marked symptoms of tetany. Infant W. was given each day 1,000 c.c. of 10:20 milk, with 5 per cent. added cane sugar. Infant H. received each day 700 c.c. of a 12:20 mixture, with 5 per cent. of added cane sugar. During the calcium chlorid periods, 2 gm. of calcium chlorid each day were added to the milk of the normal infant, and the infant with tetany was given 1.5 gm. each day.[1] The urine and stool collection periods were of three days' duration, except the fore period in the case of the infant with tetany, which, because of the active symptoms manifested, had to be abbreviated to twenty-four hours. Information as to the cause of the acid effect from calcium chlorid ingestion was sought in the data obtained from the stools. The size of this effect was estimated by means of measurements made in the urine. Bicarbonate and chlorid concentrations in the plasma were determined with the purpose of obtaining, if possible, indication of the direct cause for the lowering of the former. The effect of calcium chlorid ingestion on the excretion of fixed alkali in the urine was also directly measured. The findings are given below in the order just indicated. The methods used in obtaining them were these: Sodium, potassium, calcium and magnesium were determined in blood serum, urine and stools by the methods of Kramer and Tisdall.[2] The bicarbonate of the plasma was measured by the method of Van Slyke.[3] For chlorids in the plasma a combination of Van Slyke's plan of precipitating the protein with picric acid and Volhard's thiocyanate titration was used.[4] The procedure was essentially the same as that recently published by Myers and Short.[5] The p_H and titratable acidity of the urine were determined by the methods of Palmer and Henderson.[6] Ammonia was measured in the urine by the method of Folin and Macallum [7] and urine nitrogen by the usual Kjeldahl method.

---

[1] Holt and Howland (Diseases of Infancy and Childhood, New York, D. Appleton and Co., 1917) recommended from 30 to 60 grains (2 to 4 gm.) of calcium chlorid daily for control of the symptoms of tetany. The degree of the acid affect following the administration of calcium chlorid in usual doses may, therefore, be taken to be at least as large as was exhibited by these two infants.

[2] Kramer, B.: J. Biol. Chem. **41**:263 (Feb.) 1920. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **47**:475 (Aug.) 1921. Tisdall, F. F., and Kramer, B.: J. Biol. Chem. **48**: 1 (Sept.) 1921.

[3] Van Slyke, D. D.: J. Biol. Chem. **30**:347 (June) 1917.

THE CAUSE OF THE ACID EFFECT FOLLOWING CALCIUM CHLORID INGESTION AS INDICATED BY DATA OBTAINED FROM STOOL ANALYSES

The measurements of calcium and of chlorid found in the stools are given in Table 1. Since in this study we are concerned with the calcium ion (Ca^{++}) as the base and with the acid value of the chlorid ion (Cl^-), the amounts found have been expressed as cubic centimeters of tenth normal acid or base; e. g., the values given for calcium indicate the number of cubic centimeters of a tenth normal solution of base which could be obtained from the amounts of calcium found. That there is actually a very much larger excretion of calcium than of chlorid from ingested calcium chlorid is shown in the table. Estimated by subtracting the amount of calcium found in the stools during the fore period from the amount found when calcium chlorid was given, 60 per cent. of the added calcium was excreted in the stools in the case of the normal infant. In contrast, estimated in the same way, only 4 per cent. of the added chlorid escaped absorption. With the 220 c.c. of tenth normal calcium from added calcium chlorid there appears in the stools but 14 c.c. tenth normal chlorid. It is, therefore, evident that other base than calcium was used in the metabolism of 220 — 14 = 206 c.c. tenth normal of the 365 c.c. tenth normal chlorid given. It cannot be assumed that 206 c.c. of tenth normal of the

TABLE 1.—*Measurements of Calcium and of Chlorid in Stools: Values for Each Twenty-Four Hours*

	Infant W., Normal		Infant H., Tetany	
	Ca C.c. N/10	Cl^- C.c. N/10	Ca C.c. N/10	Cl^- C.c. N/10
Added to milk, $CaCl_2$ period	365	365	270	270
Found in stools, $CaCl_2$ period	492	31	418	94
Fore period	272	17	166	9
From added $CaCl_2$	220	14	252	85
Per cent. from added $CaCl_2$	60	4	93	32

Estimated Cl metabolized without Ca......Infant W. 207 — 14 = 193 c.c. N/10
From added $CaCl_2$..........................Infant H. 252 — 85 = 167 c.c. N/10

---

[4] The method used was an unpublished one devised by Dr. Dana W. Atchley.

[5] Myers, V. C., and Short, J. J.: J. Biol. Chem. **44**:47, 1920.

[6] Palmer, W. W., and Henderson, L. J.: Arch. Int. Med. **12**:153, 1913.

[7] Folin, O., and Macallum, A. B.: J. Biol. Chem. **11**:523, 1912.

added chlorid was absorbed without calcium. Doubtless a part of the calcium represented by this value was absorbed and then excreted through the wall of the lower intestine. Since, however, this part does not carry chlorid with it into the stools, it may correctly be included in the calcium, measuring the extent to which absorbed chlorid is left to bind other base in the body fluids. The value thus found, 206 c.c. of tenth normal, it will be seen is more than half of the administered chlorid (365 c.c. of tenth normal). In the case of the infant with tetany (Infant H.), the ingestion of calcium chlorid resulted in the production of loose stools and in consequence a much larger proportion of the ingested calcium and also of chlorid appeared in the stools (Table 1). The estimated chlorid conveyed through the body fluids and excreted without calcium was, in this instance, 252 — 85 = 167 c.c. tenth normal, again more than half of the chlorid (270 c.c. tenth normal) placed in the milk.

ESTIMATION OF THE ACID VALUE OF INGESTED CALCIUM CHLORID BY MEANS OF DATA OBTAINED FROM THE URINE

If the excess of the chlorid ion over the calcium ion absorbed were the only consequence of the addition of calcium chlorid to the food, the just estimated values for this excess could be taken as measurements of the acid effect of the calcium chlorid ingested. They would indicate that the calcium chlorid administered to these infants was, from the point of view of acid-base metabolism, an acid substance to the extent of more than half of its equivalence as hydrochloric acid. It is hardly likely, however, that other values for acid and base absorbed would be unaffected by calcium chlorid ingestion. The probability, for instance, that the absorption of phosphoric acid would be lowered as a consequence of an increased formation of insoluble calcium phosphates in the intestine has been mentioned. A measurement of the actual extent of the acid effect of calcium chlorid is best obtained by noting in the urine the extension of those factors whose purpose it is to cover an increase in the metabolism of acid as compared with that of fixed alkali.[8] Henderson[9] and Henderson and

---

[8] The term "fixed alkali" is used to distinguish the bases which are contained preformed in the food; viz., sodium, potassium, calcium and magnesium, from the base ammonia which is derived from the metabolism of protein. Although ammonia is derived from organic substances, it may not, since it does not contain carbon, be correctly called an organic base. This fact makes it necessary to use the terms fixed alkali and ammonia, rather than inorganic and organic base, in describing the metabolism of the base. The differentiation of ammonia from fixed alkali is important from the point of view of acid-base metabolism, for the reason that ammonia is biologically a toxic ion and cannot be used to appreciable extent as a base within the body, and in consequence the base concentrations of the body fluids must be composed practically entirely of fixed alkali.

[9] Henderson, L. J.: Am. Physiol. **21**:427, 1908; J. Biol. Chem. **9**:403, 1911.

Palmer[10] have shown that the extent to which acids are permitted to carry fixed alkali into the urine is controlled by (1) a regulation of the acidity of the urine, and (2) a regulated production ammonia. By the operation of these two factors of acid excretion, the base concentration of the plasma, which must be practically entirely fixed alkali, is sustained at a constant level. The necessity for this regulatory function of the kidney is indicated by the fact that even though the diet is a usual one, the quantity of acid substances claiming excretion in the urine is much larger than the intake of fixed alkali. It has been shown that this regulatory mechanism is widely extensible and will manage the excretion of large additions to the acid excretion without lowering of the base concentration in the plasma (Gamble, Ross and Tisdall[11]). Henderson[9] and Henderson and Palmer[10] have shown that a measurement of the titratable acidity of the urine plus the ammonia excretion measures the excess of acid excretion over fixed alkali excretion. The sum of these two measurements they have designated "total acid," i. e., that part of the acid excretion which has been accomplished without an expenditure of fixed alkali. Addition to the food of a substance increasing the discrepancy between the amount of acid claiming excretion and the amount of fixed alkali available for binding it in the urine should cause an equivalent extension of this "total acid" value in the urine. By the use of this principle we have undertaken to measure the acid effect of ingested calcium chlorid, using the values found for titratable acidity of the urine and ammonia excretion during the fore period as a basis from which to measure the extension of these values when calcium chlorid was given.

Table 2.—*Increase in Ammonia in the Urine Following Calcium Chlorid Ingestion*

	Ammonia in Urine			
	Fore Period, Average 24 Hours, C.c. N/10	$CaCl_2$ Period		
		1st Day, C.c. N/10	2d Day, C.c. N/10	3d Day, C.c. N/10
Infant W. (normal)	116	194	275	306
Infant H. (tetany)	53	104	141	180

Ammonia, much the larger of the two factors conserving inorganic base, was determined in the urines day by day. The values found (Table 2) indicate very clearly that ingested calcium chlorid is, from the point of view of acid-base metabolism, an acid substance. Ammonia being derived at the expense of the neutral end-product of protein

---

10. Henderson, L. J., and Palmer. W. W.: J. Biol. Chem. **17**:305, 1914.
11. Gamble, J. L.; Ross, S. G., and Tisdall, F. F.: Tr. Am. Ped. Soc. **34**:289, 1922.

metabolism, urea, an extension of the ammonia factor can be well shown by noting the increasing proportion of the total urine nitrogen which is ammonia nitrogen, when, as in this case, the metabolism of protein remains a stationary value. This often used index of the degree of an acid effect, the "ammonia coefficient," is given in Table 3. These data are from the normal infant (W.) and will satisfactorily indicate that in terms of the "ammonia coefficient" the acid effect following calcium chlorid ingestion may be designated as large.

In Table 4 are given the measurements of urinary acidity and ammonia excretion and the sum of these measurements, "total acid," found for the fore and calcium chlorid periods. Subtracting the values for the fore period from those found when calcium chlorid was given, measurements of the extension of these values and of their sum are obtained. Provided the kidney has accurately carried out its regulatory function, the increase in "total acid" should measure the increase in the excess of acid claiming excretion over available fixed alkali caused by adding calcium chlorid to the food; i. e., the acid effect following ingestion of this neutral salt. As may be seen in the table, the acid value of the ingested calcium chlorid was found to be 151 c.c. tenth normal, and 99 c.c. tenth normal, for the normal infant and the infant with tetany, respectively. These values are considerably less than those obtained for the excess of chlorid over calcium metabolized obtained from the stool analyses (Table 1); namely, 193 c.c. tenth normal and 167 c.c. tenth normal. Nevertheless, they indicate that a

TABLE 3.—*Increase in "Ammonia Coefficient" Following Calcium Chlorid Ingestion in the Case of Infant W. (Normal)*

	Fore Period, Average 24 Hours	$CaCl_2$ Period		
		1st Day	2d Day	3d Day
Total nitrogen, gm.	1.61	1.67	1.72	1.69
Ammonia nitrogen, gm.	0.16	0.27	0.39	0.43
Percentage ratio of ammonia nitrogen to total nitrogen	10	16	22	25

TABLE 4.—*Extension of the Factors Regulating Fixed Alkali Excretion Following Calcium Chlorid Ingestion: Values for Each Twenty-Four Hours*

			Values for Each 24 Hours		
Subject		p_H	Titratable Acidity, C.c. N/10	Ammonia, C.c. N/10	Total Acid, C.c. N/10
Infant W. (normal)	$CaCl_2$ period	5.5	67	258	325
	Fore period	6.2	58	116	174
	Increase		9	142	151
Infant H. (tetany)	$CaCl_2$ period	5.3	54	143	197
	Fore period	5.5	45	53	98
	Increase		9	90	99

very considerable part of the chlorid given as calcium chlorid was metabolized in the same way as would have been the case if placed in the food as hydrochloric acid. The acid equivalence of the calcium chlorid given may be estimated as $\frac{151}{365} = 0.41$ in the case of the normal infant, and for the infant with tetany as $\frac{99}{270} = 0.37$. In other words, calcium chlorid was, from the point of view of the acid-base metabolism of these infants, an acid substance to the extent of about 40 per cent. of its equivalence as hydrochloric acid.

THE DIRECT CAUSE OF THE LOWERING OF THE SERUM BICARBONATE FOLLOWING CALCIUM CHLORID INGESTION AS INDICATED BY DATA OBTAINED FROM THE BLOOD SERUM

In obtaining the foregoing estimate of the acid value of ingested calcium chlorid, the premise is used that the regulatory function of the kidney has been accurately operative in sustaining the normal total base (fixed alkali) concentration of the serum. Direct test of the accuracy of the regulation of fixed alkali excretion may be made by measuring the total concentration of fixed alkali in the blood serum. This measurement involves separate determinations of the four bases, sodium, potassium, calcium and magnesium. The recently devised methods of Kramer and Tisdall makes this a feasible project. The four measurements were made in the case of Infant H. before and after the administration of calcium chlorid, and the data obtained are given in Table 5, the values being expressed as cubic centimeters tenth normal base per hundred cubic centimeters of blood serum. The sum of the four values before and after calcium chlorid administration are approximately the same, their agreement being well within the limits of error (taken to be ± 4 per cent.) in obtaining a measurement of the total base in this way.

TABLE 5.—*Measurements of Fixed Alkali in Blood Serum from Infant H, Before and After Calcium Chlorid Ingestion*

	Before $CaCl_2$ Period, C.c. N/10 per 100 C.c.	At End of $CaCl_2$ Period, C.c. N/10 per 100 C.c.
Sodium	139.0	138.2
Potassium	6.1	5.6
Calcium	2.6	4.0
Magnesium	1.5	0.9
Total base	149.2	148.7

The significance of these data is that the metabolism of extra acid from calcium chlorid has not disturbed the concentration of the total base in the blood serum. It is, therefore, not possible to explain a lowering of bicarbonate concentration in the serum, following calcium chlorid ingestion, as a consequence of decrease in the concentration of the base. There was found, nevertheless, a marked lowering of the bicarbonate concentration in the serum in the case of both the normal infant and the infant with tetany following administration of calcium chlorid. The extent of this lowering is seen in Table 6; 24 per cent. and 21 per cent., respectively, in the case of the normal infant and of the infant with tetany. Since it is impossible to explain this decrease in bound carbonic acid as a consequence of base loss from the serum, there remains the possibility that an increase in the concentration of acid substance (or substances) has replaced a part of the bound carbonic acid. The acid value which might be expected to rise in the blood serum following calcium chlorid ingestion is obviously the chlorid ion concentration. Measurements of the chlorid concentration in serum samples from Infant H. (tetany) before and after giving calcium chlorid showed a very considerable rise in the chlorid concentration of the serum at the end of the calcium chlorid period; from 6.13 to 6.53 gm. as sodium chlorid per liter. The increase in bound hydrochloric acid was, moreover, approximately equivalent to the decrease in bound carbonic acid. The lowering of bicarbonate in the case of this infant is thus adequately explained by a rise in chlorid concentration, and assumption of a loss of the base from the serum is, therefore, not required. The data demonstrating this point are given in Table 7.

TABLE 6.—*Measurements of Bicarbonate Concentration in Serum Before and After Calcium Chlorid Ingestion*

	Infant W. (normal), per Cent. of Bound Carbon Dioxid by Volume	Infant H. (tetany), per Cent. of Bound Carbon Dioxid by Volume
Before $CaCl_2$	54.1	50.4
After $CaCl_2$	40.9	40.0
Decrease	13.2	10.4
Percentage of decrease	24	21

TABLE 7.—*Comparison of Chlorid Increase with Bicarbonate Reduction in Serum from Infant H., Before and After Calcium Chlorid Ingestion*

	Cl^-,* C.c. N/10 per 100 C.c. Serum	HCO_3^-, C.c. N/10 per 100 C.c. Serum
Before $CaCl_2$	106	23
After $CaCl_2$	112	18
	+6	—5

* Chlorids as grams NaCl per thousand cubic centimeters: Before $CaCl_2$, 6.13 gm.; after $CaCl_2$, 6.53 gm.

In order further to illustrate the manner in which increase of chlorid in the serum may be expected to diminish the concentration of bound carbonic acid, assuming that the total base remains stationary, the diagrams in Figure 1 were prepared. The left side of each of the diagrams represents the total base concentration, expressed as cubic centimeters tenth normal base per hundred cubic centimeters of serum, as determined by the four measurements given in Table 5. On the right side of the diagram, the values for the acids which bind the base in the plasma are indicated. Beginning at the top, and using the measurements given in Table 7, the concentrations of bicarbonate (HCO_3^-) and then of chlorid (Cl^-) are laid off. The sum of the usual concentrations of three other acids known to be carried in the plasma, phosphoric, sulphuric and certain organic acids, is indicated by the small block below the measurement of the chlorid (Cl^-) concentration.[12] After laying off the directly measured values for bicarbonate (HCO_3^-) and chlorid (Cl^-) and an assumed average value for the other three acids, there remains a portion of the base in the plasma in excess of the sum of these values. It is a reasonable surmise that this remainder of the total base is bound by the plasma proteins. At the reaction of blood plasma the proteins may correctly be regarded as acid substances. The diagrams indicate fairly completely the character of the acid-base composition of the plasma. It may be noted that four of the acids in the plasma, hydrochloric, phosphoric, sulphuric and the organic acids, are being conveyed for excretion in the urine and that one of them, hydrochloric acid, is carried at a comparatively huge concentration covering nearly three fifths of the total base of the plasma. This fact is striking when it is remembered that, diet being a usual one, a twenty-four hour urine specimen contains approximately the same amount of each of these four acids. The other two acid values, bicarbonate (HCO_3^-) and protein, do not under normal circumstances enter the urine. Remaining in the plasma they have to do with stabilizing the reaction of the blood. As regards the character of the base in blood plasma, the fact that it is practically entirely fixed alkali may be illustrated by stating that the concentration of ammonia in blood plasma would be approximately represented by the thickness of the line at the top of the diagram. In contrast to this minute concentration in the plasma is the fact that under usual conditions, as regards diet, from one third to one half of the base in urine is found to be ammonia. There is thus indicated the fact that the sum of the acid substances derived from a usual diet and claiming excretion in the urine is much in excess of the intake of fixed alkali, and the necessity for a regulated use of ammonia in the excretion of these acid substances in order that the base in the plasma may be sustained is apparent. The manner of the effect of an increase in the concentration of chlorid (Cl^-) on the bicarbonate (HCO_3^-) of the plasma may now, with the help of these diagrams, be briefly indicated. This effect is a consequence of the peculiar character of the concentration of bound carbonic acid, which may be described by stating that the block on the right side of the diagram indicating bound carbonic acid is automatically adjustable and will change in size following alteration of any of the other values indicated in the diagram. This adjustability is due to the fact that carbonic acid is an extremely weak acid, and also that in the plasma there is an approximately sustained level of free carbonic acid. In consequence, loss of the base will be at the expense of bicarbonate; increase of a stronger acid will obtain base from bicarbonate, and, on the other hand, if, by any means, the amount of base available for use as bicarbonate is increased it will at once be bound by the free carbonic acid.[13]

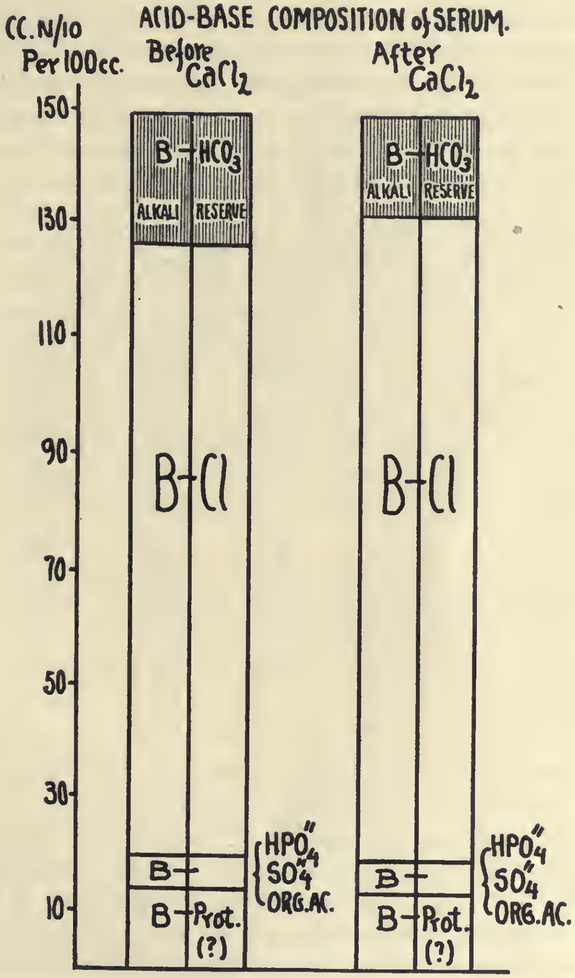
---

[12] The base bound in the plasma by the usual concentrations of the normal phosphate ion ($HPO^=$), of the sulphate ion ($SO_4^=$) and organic acids together is here taken as 6 c.c. tenth normal per hundred cubic centimeters of plasma. From published data the base bound as phosphate may be taken as 2.3 c.c. tenth normal per hundred cubic centimeters, and as sulphate as 1.7 c.c. tenth normal per hundred cubic centimeters. The concentration of the organic acids normally present in the plasma has not been accurately measured. Attempts at such a measurement in this laboratory by one of the authors (Ross), although unsatisfactory from the point of view of a sufficient accuracy, at least indicate that this concentration is a very small one. On this premise it has been assigned 2 c.c. tenth normal per hundred cubic centimeters. It may also be noted here that the base equivalence of the normal phosphate (HPO_4) per molecule indicated in the accompanying chart as 2 is actually, according to Sörensen's data, 1.8 at the usual reaction of blood plasma.

In this instance, as is illustrated in the diagram, the reduction of bicarbonate is a consequence of an increase in chlorid (Cl^-), the base remaining stationary. The fact that total base was found to remain stationary is a point of considerable physiologic significance. Obviously, a decrease in bicarbonate could be compensated for by an increase in the base concentration. Apparently, however, the mechanism regulating fixed alkali excretion serves primarily the purpose of maintaining a constant level of the base in the serum and does not raise this level in behalf of a diminished bicarbonate. In other words, the regulatory function of the kidney is not, as is often inferred, directly in support of the "alkali reserve." The maintenance of a constant level of total base is thus indicated as a matter of greater importance than maintenance of the bicarbonate concentration at its usual size. The necessity for a constancy of the total base concentration is understandable from the fact that, owing to the adjustability of the value for bound carbonic acid, it is the size of the base concentration which determines the total salt content of the plasma. The osmotic pressure of the plasma may, therefore, be said to be closely dependent on the mechanism sustaining the base concentration. It is difficult to imagine means of extensive compensation for the effect on osmotic pressure of alterations in the base concentration. The relatively less necessity for a constancy of bicarbonate concentration is understandable because of the known

---

[13] In this discussion the adjustability of the acid side of the accompanying chart to the base level is attributed entirely to the elasticity of the bicarbonate concentration. This is practically the case. It should be mentioned, however, that the phosphate and proteinate values (in terms of base bound) are not to be regarded as immovable in the presence of strong acids claiming base. Secondary phosphate and the proteinates being salts of weak acids will tend to supply the base at the expense of a shift in reaction due to release of acid phosphate and protein. In the case of bicarbonate the tendency to shift of reaction is rapidly offset by removal of carbonic acid by way of the lungs. It is owing to this fact chiefly that bicarbonate supplies nearly all of the base for neutralization purposes; i. e., it practically constitutes the "alkali reserve."



Acid-base composition of blood serum from Infant H. before, and the third day following, calcium chlorid administration. Constructed from measurements of base given in Table 5 and of chlorin and bicarbonate in Table 7, to illustrate reduction of the alkali reserve caused by increase in the chlorid (Cl^-) concentration.

extensibility of the other factors concerned in neutrality regulation (circulatory and respiratory) in compensation for a lowered alkali reserve.

THE SIGNIFICANCE OF AN INCREASED EXCRETION OF FIXED ALKALI IN THE URINE FOLLOWING CALCIUM CHLORID ADMINISTRATION

The measurements of the total base in the blood serum from Infant H. given above constitute evidence that the excretion of the extra acid when calcium chlorid was given was managed without appreciable depletion of the base concentration of the body fluids. In making this statement the premise is used that a normal concentration of the base in the serum may be taken to indicate that the concentrations of base in other inaccessible portions of the body water cannot be greatly altered. In apparent contradiction of this inference from the base measurements in the serum, there was found in the urine from both infants a moderately large increase in fixed alkali excretion during the calcium chlorid periods. This extra base includes, only in the instance of Infant W., and to a very slight extent, the base calcium which was added to the intake. The size and composition of this increased base excretion in the urine are shown in Table 8. The table also includes measurements of the base contained in the stools, and it will be seen that the amounts are larger for each of the four bases during the calcium chlorid periods. The increased excretion chiefly of sodium and potassium in the urine was, therefore, not a consequence of an increased absorption. Does this large increase in fixed alkali excretion in the urine measure a failure of the kidney to sustain correct base concentrations in the body fluids? Were it permissible to assume that the

TABLE 8.—*Excretion of Inorganic Base Before and Following Calcium Chlorid Ingestion: Values for Each Twenty-Four Hours*

Base	Infant W.		Infant H.	
	Fore Period, C.c. N/10	$CaCl_2$ Period, C.c. N/10	Fore Period, C.c. N/10	$CaCl_2$ Period, C.c. N/10
Urine:				
Sodium	55.2	84.8	14.7	99.1
Potassium	103.0	110.0	110.0	96.4
Magnesium	1.2	3.4	2.5	5.0
Calcium	2.8	17.5	4.0	4.5
Total	162.2	215.7	131.2	205.0
Increase	.....	53.5	.....	73.8
Stools:				
Sodium	16.1	20.0	4.4	43.5
Potassium	40.0	62.0	19.7	49.5
Magnesium	22.5	46.7	22.5	35.0
Calcium	272.0	492.0	166.0	418.0
Total	350.6	620.7	212.6	546.0
Increase	.....	270.1	.....	333.4
Total excretion	513	836	343	751
Total increase	...	324	...	408
Base added (calcium)	...	365	...	270

volume of body water remained the same during the two experimental periods, such an inference would be unavoidable. It is a nearly certain premise, however, that the ingested calcium chlorid would exert a diuretic effect, with consequent decrease in the volume of body water. A reduction of body water would provide a quantity of inorganic base for use in the process of acid excretion without disturbance of the base concentrations in the remaining body fluids. With the evidence from Infant H. of a correctly sustained base level in the serum, it would seem reasonable to regard the increased base excretion as probably entirely a consequence of the diuretic effect of calcium chlorid. As indication that there was probably a considerable loss of body water, the increase in volume of urine during the calcium chlorid periods may be noted. During the fore period of Infant W., the average twenty-four hour volume of urine was 420 c.c., and during the calcium chlorid period this value was found to be 510 c.c. Infant H. voided only 270 c.c. the day before calcium chlorid administration. The average twenty-four hour urine volume for the three following days was 390 c.c. This large increase in the volume of urine is especially significant since it occurred in the presence of a considerable loss of water in the stools.[14] In definite agreement with the postulation of a loss of body water during the periods of calcium chlorid administration, losses in body weight were in both instances measured, Infant W. losing 90 gm., and Infant H., 300 gm.

As an objection to the inference of a loss of body water in explanation of the increased excretion of sodium, potassium and magnesium, it might be argued that the increased excretion of these bases was offset by an increased retention of the added base calcium. It may, indeed, be derived from the data in Table 8 that in the case of Infant W. the increased retention of calcium was larger than the combined increase in excretion of the three other bases. This increase in calcium retention may be estimated by subtracting the increase in excretion from the calcium added to the milk, thus, from Table 8, 510 — 275 = 235 c.c. tenth normal increase in excretion of calcium when calcium chlorid was given. Subtracting this value from the 365 c.c. tenth normal calcium added to the intake during this period, 130 c.c. tenth normal calcium is indicated as the increase in calcium retention following calcium chlorid administration. The increased excretion of the other three bases was 327 — 238 = 89 c.c. tenth normal and was, therefore, more covered by the increased retention of calcium. It would be almost certainly incorrect, however, to assume that the retained calcium replaced in the body water the lost sodium, potassium and magnesium. Calcium being held at a constant and relatively very small concentration, it is scarcely likely that in this normal infant this level would be raised. In all probability the extra calcium retained was added to the calcium deposits of the body. In the case of Infant H., owing largely to the loose stools, the increase in the excretion of sodium, potassium and magnesium (155 c.c. tenth normal) was greatly in excess of the slight increase in calcium retention (17 c.c. tenth normal). Insomuch as sodium, potassium and magnesium, in contrast to calcium, are presumably present in the body entirely in solution in the body water, it seems reasonable to infer a reduction of the volume of body water from an increased excretion of these bases, provided evidence can be found, as in this instance, indicating that base concentrations in the body fluids have been correctly sustained. We are thus led to conclude that the acid effect of calcium chlorid; i. e., the increase in the excess of acid over fixed alkali claiming excretion, is probably entirely covered (and completely measured) by the increase in the titratable acidity of the urine, together with the increased ammonia excretion, and that the extra base found in the urine is a consequence of reduction of the volume of body water and does not represent depletion of base concentration within the body. The indicated ability of the kidney to sustain a constant base concentration in the body fluids under circumstances causing both a large alteration in the excess of acid over base claiming excretion and a considerable change in the volume of body water is worth admiring.

---

[14] The stools of Infant H. (tetany) were, during the fore period, small in amount, formed and dry. During the calcium chlorid period they became definitely diarrheal in character and contained 140 c.c. of water each twenty-four hours. The stools of Infant W. (normal) contained rather more than a usual amount of water, during both the fore and the experimental periods, their water content for each twenty-four hours being 70 c.c. and 110 c.c., respectively, during the two periods.

The importance of taking into account in any study of the metabolism of inorganic substances the possibility of alterations of the volume of body water is, we believe, worth emphasizing. Particularly in the case of sodium, potassium, chlorid and phosphate,[15] because of the high concentrations at which these ions are held in the body fluids, a marked alteration of the amounts eliminated will be a necessary consequence of relatively slight changes in the volume of body water. That fluctuation of this value is not an improbability is indicated by the irregularities of the day to day weight curve of a normal infant. In the case of malnourished infants these irregularities are often of such size as must very greatly effect the amounts of inorganic substances eliminated. That this factor will largely determine the excretion of inorganic substances, especially those mentioned above, following ingestion of unusual amounts of various salts, would seem to be altogether probable. It is our impression that many of the data obtained to represent the metabolism of the minerals have been incorrectly interpreted from failure to take into account the possibility of alterations of the volume of body water. Particularly do we wish to emphasize the incorrectness of inferring an alteration of concentrations within the body from the finding of an increase or decrease in elimination.

---

[15] The conspicuous size of the chlorin concentration may be seen in the accompanying chart. The even larger concentration of sodium may be indicated by the statement that it constitutes 92 per cent. of the base in blood plasma. Katz' (Arch. f. d. ges. Physiol. **63**:18, 1896) measurements of the inorganic constituents of fresh human muscle demonstrate that potassium is the chief base in muscle water and also indicate a considerable concentration of phosphates in this compartment of body water.

CONCLUSIONS

The following conclusions as regards the effect of calcium chlorid ingestion on acid-base metabolism are offered with the reservation that they rest upon data obtained from but two infants.

Ingested calcium chlorid in consequence of the relatively much greater absorption of the chlorid ion (Cl^-) than the calcium ion (Ca^{++}) behaves as does an acid substance. The effect on acid-base metabolism of the ingestion of 1 gm. of calcium chlorid may be described as of the same extent as would be produced by placing in the milk 75 c.c of tenth normal hydrochloric acid. The considerable increase in the excess of acid over fixed alkali claiming excretion in the urine is apparently accurately compensated for by an increase in urinary acidity and of ammonia excretion, with the result that the normal base concentration of the blood plasma is sustained. The lowering of bicarbonate following calcium chlorid ingestion is, therefore, not a consequence of depletion of the plasma base. It is found to be due to a rise in chlorid (Cl^-) concentration, displacing an equivalence of bound carbonic acid.

Following calcium chlorid ingestion there occurs a moderately large increase in the excretion of fixed alkali, especially of sodium and potassium in the urine. This is correctly to be regarded as a consequence of a reduction of the volume of body water, and not as indicating withdrawal of base from body fluids.

The total base concentration of the serum is sustained at a constant level by a remarkably accurate regulation of fixed alkali excretion in the urine. This regulation is successfully accomplished in the presence both of a large increase in the excess of acid over base claiming excretion and of a considerable change in the volume of body water. It is to be noted, moreover, that the normal total base concentration is not altered in behalf of a lowered bicarbonate.

STUDIES OF TETANY

II. THE EFFECT OF INGESTION OF HYDROCHLORIC ACID PRODUCING SUBSTANCES ON THE ACID-BASE METABOLISM OF AN INFANT AND THE PROBABLE MANNER OF THEIR ACTION IN THE TREATMENT OF TETANY *

J. L. GAMBLE, M.D.
BOSTON
AND
G. S. ROSS, M.D.
Cooper Traveling Fellow, McGill University
MONTREAL

The data presented in this paper were obtained from an infant with tetany who was given, at intervals, ammonium chlorid, hydrochloric acid, the usual agent, calcium chlorid, and calcium acetate, a substance differing from the other three in that presumably it does not produce an acid effect. The purposes of this study may be briefly indicated by the headings, which will be used in the following order in presenting and discussing the information obtained.

1. Evidence indicating that an acid effect, due to an increased metabolism of hydrochloric acid, following the administration of calcium chlorid, ammonium chlorid or hydrochloric acid is a factor in the therapeutic efficacy of these substances in tetany.
2. Data illustrating the regulated use of fixed alkali in the process of acid excretion.
3. The manner of the effect of an increased metabolism of hydrochloric acid on the excretion in the urine of other acid substances and of fixed alkali.
4. The manner of the effect of an increased metabolism of hydrochloric acid on the plasma bicarbonate.
5. The reaction of the plasma in the presence of an increased metabolism of hydrochloric acid.
6. The probable manner of a therapeutic effect in tetany following the administration of substances producing an increased metabolism of hydrochloric acid.

The infant upon whom this study was made was a fairly well developed and well nourished colored boy, 13 months old, weighing 19 pounds. He presented slight evidences of rickets, which were confirmed by roentgenographic examination. He entered the hospital with an acute otitis media, exhibiting at the same time marked manifestations of tetany. Occasional "spasms" had been noted during the month

---

* Received for publication, March 21, 1923.

* From the Department of Pediatrics, Johns Hopkins University, Baltimore.

preceding admission to the hospital. Following an incision of the right ear drum, the symptoms of an acute infection rapidly disappeared, but those of tetany persisted. For the first three days of his stay in the hospital, owing to the general symptoms from the acute otitis media, he was given as food only small amounts of diluted milk. Beginning the fourth day after admission and continuing throughout the long period of observation (nearly eight weeks), the food given was a liter of whole milk each day, with the addition, during the last ten days of his stay in the hospital, of cod liver oil, orange juice and farina.

1. EVIDENCE INDICATING THAT AN ACID EFFECT, DUE TO AN INCREASED METABOLISM OF HYDROCHLORIC ACID, FOLLOWING THE ADMINISTRATION OF CALCIUM CHLORID, AMMONIUM CHLORID AND HYDROCHLORIC ACID IS A FACTOR IN THE THERAPEUTIC ACTION OF THESE SUBSTANCES IN TETANY

Demonstration[1] that calcium chlorid, the agent most frequently used in the treatment of infantile tetany, behaves within the body to a large extent as an acid substance suggests that an acid effect caused by this substance may be a factor in its therapeutic action in tetany. An obstacle to this inference is the fact that the calcium content of the plasma is increased by the administration of calcium chlorid. The marked decrease in the calcium of the blood plasma, which is quite specifically characteristic of active tetany,[2] and the well founded probability of a relationship of the ionized fraction of the calcium in the body fluids to the control of neuromuscular irritability[3] make necessary the admission that the therapeutic action of calcium chlorid may be entirely a consequence of the increased calcium concentration which it causes. The possibility of an acid effect from this salt being also a factor in the therapeutic result can obviously best be tested by the administration of substances which may be expected to produce an acid effect of the same character as that produced by calcium chlorid, without, at the same time, raising the calcium content of the plasma. Since J. B. S. Haldane[4] has recently demonstrated that ammonium chlorid is metabolized to a large extent as hydrochloric acid, probably by reason of the ammonia being conveyed through the body fluids in the form of the neutral substance urea, this salt would seem to be exactly suitable for testing the possibility that the acid effect noted in the case of calcium chlorid administration is a factor in the relief of the symptoms of tetany. Presumably, the character of the acid effect produced by calcium chlorid and ammonium chlorid would be the same as would follow placing hydrochloric acid in the milk.

---

[1] Gamble, J. L., Ross, G. S., and Tisdall, F. F.: Studies of Tetany. I. The Effect of Calcium Chlorid Ingestion on the Acid Base Metabolism of Infants, Am. J. Dis. Child., this issue, page 455.

[2] Howland, J., and Marriott, W. McK.: Quart. J. Med. **11**:289 (July) 1918.

[3] Reiss, E.: Ztschr. f. Kinderh. **3**:1, 1911; MacCallum and Voegtlein: J. Exper. Med. **11**:118, 1909; Loeb, J.: J. Biol. Chem. **23**:423, 1915.

[4] Haldane, J. B. S: J. Physiol. **55**:265 (Aug.) 1921.

While we were proceeding to test the therapeutic value of the acid effect from calcium chlorid by the administration of ammonium chlorid and of hydrochloric acid to the subject of this study, papers by German investigators demonstrating the therapeutic action in tetany of both ammonium chlorid and hydrochloric acid came to hand. The point was quite thoroughly tested by Scheer,[5] using a "hydrochloric acid milk" and by Freudenberg and György[6] by the administration of ammonium chlorid. The data from the subject of this study are, as regards the therapeutic effect from the administration of either of these substances, in agreement with the much more extensive evidence presented by these workers. The data on this point are given in Table 1. It will be seen that the administration of ammonium chlorid and of hydrochloric acid caused a complete disappearance of the evidences of increased neuromuscular irritability. As regards the amounts of these substances given, it may be said that they are the equivalents, on the basis of chlorin content, of a fairly large dose of calcium chlorid.[7] Following the brief periods of administration, there occurred, in both instances, an almost immediate reappearance of the manifestations of active tetany. It is to be noted that the ingestion of hydrochloric acid was followed by an increase in the calcium content of the blood serum and that this increase was approximately of the same magnitude as followed the administration of calcium chlorid in an amount equivalent on the basis of chlorid (Cl^-) content. This effect from hydrochloric acid is doubtless due to an increased absorption of calcium as calcium chlorid produced in the milk at the expense of the dicalcium and tricalcium phosphates. This point was appreciated by Scheer,[5] and he assumed correctly that the placing of hydrochloric acid in milk would in this indirect manner bring about an increase in the calcium content of serum. It is apparent, however, that this fact obstructs the inference that an acid effect from hydrochloric acid ingestion is also a factor in the therapeutic result. On this point, however, the evidence is clear in the case of ammonium chlorid. It may be seen in the table that there occurred an actual diminution of the calcium content of the serum during the period of ammonium chlorid administration. The absence of an augmenting effect on the calcium content of the serum following ammonium chlorid ingestion is understandable; hydrochloric acid being presumably derived from this salt only after it is absorbed and thus too late to bring about an increased absorption of calcium as calcium chlorid. The fact demonstrated by Freudenberg and György[6] that the ingestion of ammonium chlorid will relieve the symptoms of tetany may, therefore, be taken as clearly indicating a process which is independent of the size of the calcium concentration in the serum. The outstanding consequence of ingesting ammonium chlorid is a large

---

[5] Scheer, K.: Jahrb. f. Kinderh. **97**:130 (Feb.) 1922.

[6] Freudenberg, E., and György: Klin. Wchnschr. **1**:410 (Feb. 25) 1922.

[7] The dose of calcium chlorid for each twenty-four hours, usual in the treatment of tetany, is from 2 to 4 gm. The 4 gm. calcium chlorid given this infant contains of chlorin, 2.6 gm., or 730 c.c. tenth normal. Of this, 40 per cent. (290 c.c. tenth normal) may, on the basis of the data given in the preceding paper (Footnote 1), be regarded as hydrochloric acid. The 4 gm. of ammonium chlorid given also provides an intake of 2.6 gm. of chlorin or 730 c.c. tenth normal, all of which, however, as will appear in this paper, is probably metabolized as hydrochloric acid. In demonstrating the therapeutic efficacy of this salt Freudenberg and György gave from 3 to 6 gm. The hydrochloric acid given was in terms of normality, 750 c.c. tenth normal; i. e., approximately the same amount as was assumed to be derived from 4 gm. ammonium chlorid. This is a several times larger dose than was used by Scheer, 260 c.c. tenth normal. It is of interest to note that the amount of hydrochloric acid which Scheer gave corresponds roughly to the estimated hydrochloric acid production from 4 gm. of calcium chlorid (compare the foregoing).

TABLE 1.—*Therapeutic Effect in Tetany of the Administration of Ammonium Chlorid and Hydrochloric Acid*

Date	Treatment	Electrical Reactions		Ca in Blood Serum, Mg. per 100 C.c.	Clinical Signs of Tetany
		Anodal Opening, Milliamperes	Cathodal Opening, Milliamperes		
May 2	....	2.8	4.4		
May 3	....	2.4	4.4		
May 6	NH_4Cl 4 gm.	1.8	3.0	7.1	
May 7	NH_4Cl 4 gm.	3.4	>5.0	...	Chvostek sign present
May 8	NH_4Cl 4 gm.	>5.0	>5.0	6.9	
May 9	....	>5.0	>5.0	6.4	Chvostek sign not present
May 10	....	2.4	3.0	...	Chvostek sign marked
May 11	$CaCl_2$ 4 gm.	2.2	3.8	5.2	Chvostek sign, laryngeal stridor
May 12	$CaCl_2$ 4 gm.				
May 13	$CaCl_2$ 4 gm.	4.8	>5.0	8.0	Slight Chvostek sign
May 14	....	>5.0	>5.0	...	No Chvostek sign
May 15	....	2.8	4.0	...	Chvostek sign present
May 16	....	1.8	2.4	5.0	Chvostek sign, laryngeal stridor
May 17	....	.....	3.0		
May 18	Ca acetate 5.0 gm.				
May 19	Ca acetate 6.3 gm.	2.4	4.4		
May 20	Ca acetate 6.3 gm.	3.2	>5.0	6.6	
May 21	....	>5.0	>5.0	...	Slight Chvostek sign
May 22	....	2.2	4.6		
May 24	Ca acetate 6.3 gm.	1.8	3.6	5.9	
May 25	Ca acetate 6.3 gm.	2.2			
May 26	Ca acetate 6.3 gm.	1.6	>5.0		
May 27	Ca acetate 6.3 gm.	1.4	>5.0		
May 28	....	3.4	>5.0	6.9	Chvostek sign slightly positive
May 29	....	2.0	>5.0		
June 5	HCl 2.72 gm.*	.....	.....	5.0	Cathodal closure tetanus below 5 milliamperes
June 6	HCl 2.72 gm.*.......	>5.0	>5.0		
June 7	....	>5.0	>5.0	7.6	Slight Chvostek sign
June 8	....	>5.0	>5.0		
June 9	....	2.8	>5.0	...	Marked Chvostek sign
June 10	Cod liver oil, farina and orange juice	2.8	>5.0	5.6	
June 17	Cod liver oil, farina and orange juice	>5.0	>5.0	...	Chvostek sign just obtainable
June 20	Cod liver oil, farina and orange juice	.....	.....	...	No Chvostek sign
June 24	Cod liver oil, farina and orange juice	>5.0	>5.0	9.7	No Chvostek sign

* Obtained by placing 75 c.c. tenth normal HCl in milk.

increase in the metabolism of hydrochloric acid. It would, therefore, seem highly probable that the therapeutic action of ammonium chlorid is in some way a result of an alteration of acid-base values caused by metabolism of an unusually large amount of hydrochloric acid, and that calcium chlorid or hydrochloric acid placed in the milk will exert an effect identical in this respect with that following the ingestion of ammonium chlorid.

As indirect evidence that an acid effect may be a factor of importance in relieving the symptoms of tetany may be cited the fact obtained from clinical experience that calcium chlorid has a greater therapeutic efficacy than calcium acetate. The acid portion of the latter being oxidizable, ingestion of this salt would not be expected to exert an effect on the acid-base values within the body. We noted, with F. F. Tisdall,[1] a reduction of the plasma bicarbonate following the ingestion of calcium chlorid. Measurements of the plasma bicarbonate were obtained from the subject of this study two days and again four days after beginning calcium acetate therapy. The values found were 53.2 and 51.3 per cent. of carbon dioxid bound by volume; i. e., not appreciably less than the usual value. It may also be noted as regards the comparative efficacy of this salt that it produced a much less marked rise in the calcium content of the serum than did calcium chlorid, presumably indicating a better absorption of calcium chlorid. The amount of calcium given as calcium acetate was the same as was contained in the calcium chlorid given. It is interesting to note that hydrochloric acid produced a greater rise in the calcium content of the serum than did the calcium containing salt (calcium acetate).

It is worth noting that following cessation of the administration of the agents used there was, in every instance, a prompt recurrence of the manifestations of tetany. The impression is obtained that these agents resist rather than remove the underlying cause of the tetany. Following the reappearance of symptoms after the hydrochloric acid period, the infant was given cod liver oil, orange juice and farina. On this mixed diet the evidences of tetany soon disappeared, and did not recur during the remainder of his stay in the hospital. The effect of these additions to the diet must be in its manner quite different from that of the hydrochloric acid producing substances, and probably may be regarded as, in a correct sense, curative.

2. DATA ILLUSTRATING THE REGULATED USE OF FIXED ALKALI IN THE PROCESS OF ACID EXCRETION

Since the administration of calcium chlorid, ammonium chlorid or hydrochloric acid amounts, from the point of view of acid-base metabolism, to a large increase in the intake of acid (hydrochloric acid), an outstanding question for consideration is the possibility that metabolism of an unusually large amount of this acid may cause an alteration of the base concentrations in the body fluids. The importance of accurately sustained base concentrations within the body has been indicated in the preceding paper.[1] It may be said that the normal structure, in a physicochemical sense, of the body fluids, for example, their osmotic pressure and reaction, is closely dependent on a careful regulation of the extent to which acid substances are permitted to carry fixed alkali into the urine. Even under normal circumstances, fixed alkali must be used in the process of acid excretion with a carefully regulated economy, the total of acid substances claiming excretion in the urine being greatly in excess of the fixed alkali content of usual diets. The administration of hydrochloric acid for a therapeutic purpose provided opportunity for observation of the process of acid excretion under circumstances calling for a very unusual extension of the factors conserving the base content of the body fluids. An understanding of the mechanism accomplishing the regulation of fixed alkali excretion and an appreciation of its very great extensibility are indispensable in a consideration of the effect on the acid-base metabolism of greatly increasing the acid intake. We have, therefore, thought it worth while to describe here in some detail the process of acid excretion and to obtain from the urine following administration of ammonium chlorid and hydrochloric acid such measurements as will serve fairly completely to display in quantitative terms all of the factors in this regulatory function of the kidney.

TABLE 2.—*Concentration of Base in Water of Blood Serum and in Water of Muscle Tissue* *

Base	Serum Water, C.c. Tenth Normal per Hundred C.c.	Muscle Water, C.c. Tenth Normal per Hundred C.c.
Sodium	157.7	45.8
Potassium	5.6	108.1
Calcium	5.5	4.9
Magnesium	2.7	23.3
Total	171.5	182.1

* The values for serum water were computed from the average usual amounts of the bases in blood serum by taking the water content of serum as 91 per cent. We are indebted to Kramer and Tisdall for the data used. In obtaining the concentrations given for muscle water Katz' (Footnote 8) measurements of the amounts of the bases in fresh human muscle tissue were used, the water of muscle tissue being taken as 76 per cent.

The character of the base concentrations of the body fluids may first be briefly described. They are composed practically entirely of the sum of the concentrations of sodium, potassium, calcium and magnesium. The base ammonia which binds a large part of the total acid value in the urine is not used to appreciable extent in the body fluids. It is this fact that base concentrations within the body must be composed entirely of fixed alkali which makes necessary a careful regulation of the use of fixed alkali in the process of acid excretion. The base concentration which is accessible to measurement is that of blood plasma. Estimations of the base in the water of muscle tissue, derived from the data of Katz[8] and given in Table 2, will serve to indicate the probability that the base concentrations in various compartments of body water are of a closely similar size. In this comparison of the base content of an example of extracellular body water with that found in an intracellular portion, it is interesting to note that, although the total base content is roughly the same in both, the concentrations of the individual bases are, except in the case of calcium, widely different; sodium, constituting most of the base in blood serum, and potassium, the greater part in muscle water. The significance of the total concentration (as a controlling factor in the osmotic pressure mechanism) is thus evidently quite apart from the local physiologic purposes of the concentrations of the individual bases.

We are chiefly indebted to L. J. Henderson[9] for our knowledge of the factors which control the extent to which fixed alkali is used in the process of acid excretion. Briefly stated, this regulation depends on the ability of the kidney to secrete a fluid more acid than blood plasma and on a regulated production of ammonia. As regards the locus of this regulated ammonia production, Nash and Benedict[10] have presented good, though perhaps not conclusive, evidence and argument that it takes place in the kidney. Ammonia is, in effect, substituted, as the acid substances enter the urine, for fixed alkali which they bound while being conveyed in the body fluids. The acidity of the urine, on the other hand, represents an absolute saving of base, owing to the fact that certain acid substances bind less base in the urine than they do while being carried in the body fluids. The acid substances which are excreted with less base than they bind while being carried to the kidney are phosphoric acid and organic acids. The base saving in this manner in the elimination of phosphoric acid may be briefly described. Phosphoric acid is present in the body fluids and in urine in the form of both its monobasic and its dibasic salts. In the faintly alkaline blood plasma, much the greater part of the acid is bound as dibasic phosphate (B_2HPO_4). In very acid urine, on the other hand, nearly all of the phosphoric acid is present as monobasic phosphate (BH_2PO_4).[11] The excretion of phosphoric acid in very acid urine is thus accomplished with an expenditure of slightly more than half of the base which it bound while being carried to the kidney. Organic acids, by reason of the fact that they are weakly acid substances, may be present to a slight extent unbound at the usual reaction of urine, whereas at the faintly alkaline reaction of blood plasma they must be practically entirely bound. The two remaining urinary acids, hydrochloric and sulphuric, being "strong" acids, i. e., dissociating when in solution practically all of their hydrogen, cannot be present to any appreciable extent in a fluid of such relatively low hydrogen ion concentration as is even very acid urine. These two acids must, therefore, carry their complete equivalence of base into the urine. The acidity of the urine being due chiefly to acid phosphate and slightly, under normal circumstances of metabolism, to free organic acids, the economy of base in the elimination of these substances may, as L. J. Henderson suggested, be easily measured by titrating the urine to the reaction of blood plasma (p_H 7.4), the amount of base which must be added to the urine in order to bring it to the faintly alkaline reaction of the plasma being obviously a measure of the base which these substances left behind in the plasma.

---

[8] Katz: Arch. f. d. ges. Physiol. **63**:18, 1896.

[9] Henderson, L. J.: Am. J. Physiol. **21**:427, 1908; J. Biol. Chem. **9**:403, 1911; Henderson, L. J., and Palmer, W. W.: J. Biol. Chem. **17**:305, 1914.

[10] Nash, T. P., and Benedict, S. R.: J. Biol. Chem. **48**:463 (Oct.) 1921.

[11] *B* in these formulas represents an atom of univalent base.

TABLE 3.—*Indirect Estimation of Fixed Alkali Excretion Illustrating Relationships of the Factors Concerned in the Process of Acid Excretion*

Indirect Measurement of Fixed Alkali Excretion	
Acid excretion in terms of base bound at p_H 7.4:	
Organic acids, directly titrated	= 167 c.c. tenth normal organic acids
Sulphates; 180 mg. sulphur ÷ 3.2 × 2	= 115 c.c. tenth normal H_2SO_4
Phosphates, 381 mg. phosphorus ÷ 3.1 × 1.8	= 223 c.c. tenth normal H_3PO_4
Chlorids, 1,645 mg. chlorin ÷ 3.5	= 470 c.c. tenth normal HCl
	975 c.c. tenth normal total acid excretion
Titratable acidity of urine	= 96 c.c. tenth normal "base economy"
	879 c.c. tenth normal total base excretion
Ammonia, 982 mg. ammonia ÷ 1.7	= 375 c.c. tenth normal NH_3
	504 c.c. tenth normal fixed alkali excretion
Direct Measurement of Fixed Alkali Excretion (Neglecting Magnesium)	
Sodium, 435 mg. ÷ 2.3	= 189 c.c. tenth normal
Potassium, 1,150 mg. ÷ 3.9	= 295 c.c. tenth normal
Calcium, 8 mg. ÷ 4 × 2	= 4 c.c. tenth normal
Total	= 488 c.c. tenth normal

* Data from urine specimen obtained during the first twenty-four hours of hydrochloric acid administration.

We have undertaken to obtain from twenty-four hour urine specimens, collected from this infant during and following the administration of hydrochloric acid and of ammonium chlorid, measurements of the factors controlling fixed alkali excretion and also of the extent to which they have limited the conveyance of fixed alkali into the urine. The latter value was estimated indirectly by subtracting from the total acid excretion (expressed in terms of base bound by the acid substances at the reaction of blood plasma) the sum of the measurements of the titratable acidity of the urine and the ammonia excretion, the value for the total acid excretion being obtained by making separate measurements of the acid substances in the urine; namely, hydrochloric, sulphuric, phosphoric and organic acids. The base bound by phosphoric acid at the reaction of the plasma is taken, on the basis of Sörensen's data, as 1.8 times the molecular concentration of monohydrogen phosphate ($HPO_4^=$).[12] The organic acids are assumed to bind the equivalence of their titration value, as determined by the method of Van Slyke and Palmer. Hydrochloric acid binds one, and sulphuric acid, owing to the divalency of its acid radicle, two equivalents of base. This plan of indirect measurement of fixed alkali excretion by subtracting the titratable acidity of the urine and its ammonia content from the total acid excretion is illustrated in Table 3. Estimation of the fixed alkali excretion in this indirect manner is much easier to accomplish than by direct measurements of the amounts of sodium, potassium, calcium and magnesium in the urine, the methods for determining the bases being more laborious than those by means of which the acid values are obtainable. Our chief purpose, however, in using this plan was to display all of the acid-base factors in the urine and thus to illustrate completely, by means of quantitative data, the process of acid excretion. The value for the fixed alkali excretion obtained in this way cannot be regarded as more than an approximately accurate estimation. That the principles involved are substantially correct and that the result obtained is of an accuracy quite sufficient for illustrative purposes are indicated by the value found for the fixed alkali excretion directly measured in the same specimen (Table 3). This measurement does not contain magnesium and is, therefore, slightly, probably not more than from 2 to 4 c.c. tenth normal, incomplete. It will be seen to agree very satisfactorily with the indirectly determined value.

Data obtained in the manner just described from twenty-four hour specimens of urine collected during and following the administration of ammonium chlorid and of hydrochloric acid are given in Tables 4 and 5. As a basis from which to note the effect of hydrochloric acid ingestion on acid-base values in the urine, a specimen obtained several days before giving hydrochloric acid was also analyzed. A specimen was, for the same purpose, collected the day before administration of ammonium chlorid. The data from this specimen are not given, as it was found that they were for the most part much smaller values than were obtained from the specimen collected before the hydrochloric acid period. This is believed to have been due to an unusual retention of food substances in consequence of the fact that this was the first day

---

[12] According to Sörensen's measurements, in a solution of p_H 7.4 and containing salts of phosphoric acid, 20 per cent. of the monohydrogen phosphate (HPO_4) is bound as BH_2PO_4 and 80 per cent. as B_2HPO_4. The base (B) bound by phosphoric acid at p_H 7.4 is, therefore, $0.2 + (0.8 \times 2) = 1.8$ times the molecular concentration of the monohydrogen phosphate ion.

Table 4.—*Acid and Base Excretion Following Ingestion of Ammonium Chlorid*

Day of Experiment	Volume C.c.	p_H	Acid Excretion in Terms of Base Bound in Plasma					Base Economy (Titr. Acid) C.c. Tenth Normal	Total Base Excretion, C.c. Tenth Normal	Ammonia Excretion, C.c. Tenth Normal	Fixed Base Excretion, C.c. Tenth Normal	Creatinin, C.c. Tenth Normal
			Organic Acids, C.c. Tenth Normal	H_2SO_4 C.c. Tenth Normal	H_3PO_4 C.c. Tenth Normal	HCl C.c. Tenth Normal	Total Acid Excretion, C.c. Tenth Normal					
1. 750 c.c. tenth normal NH_4Cl	410	6.2	131	103	198	278	**710**	88	622	301	**321**	115
2. 750 c.c. tenth normal NH_4Cl	790	5.8	153	114	261	945	**1,473**	149	1,324	577	**747**	118
3. 750 c.c. tenth normal NH_4Cl	550	5.8	156	123	189	822	**1,290**	112	1,178	786	**392**	108
4. No NH_4Cl	760	6.5	146	90	147	491	**874**	46	828	576	**252**	105
5. No NH_4Cl	750	6.5	148	116	170	230	**664**	54	610	224	**386**	102

Table 5.—*Acid and Base Excretion Following Hydrochloric Acid Ingestion*

Day of Experiment	Volume C.c.	p_H	Acid Excretion in Terms of Base Bound in Plasma					Base Economy (Titr. Acid) C.c. Tenth Normal	Total Base Excretion, C.c. Tenth Normal	Ammonia Excretion, C.c. Tenth Normal	Fixed Base Excretion, C.c. Tenth Normal	Creatinin, C.c. Tenth Normal
			Organic Acids, C.c. Tenth Normal	H_2SO_4 C.c. Tenth Normal	H_3PO_4 C.c. Tenth Normal	HCl C.c. Tenth Normal	Total Acid Excretion, C.c. Tenth Normal					
1. No HCl	440	6.8	145	100	192	233	**670**	33	637	230	**407**	106
2. 750 c.c. tenth normal HCl	650	6.2	167	115	223	470	**975**	96	879	375	**504**	130
3. 750 c.c. tenth normal HCl	790	5.9	171	115	279	1,000	**1,565**	145	1,420	688	**732**	126
4. No HCl	530	6.4	158	96	194	510	**958**	72	886	568	**318**	121
5. No HCl	560	6.8	149	91	174	312	**726**	31	695	380	**315**	115
6. No HCl	450	6.7	125	99	166	228	**618**	34	584	198	**386**	107

of the period during which a liter of whole milk was given, following a very inadequate food intake. The data from the specimen collected the second day following cessation of ammonium chlorid administration are approximately of the same values as those from the foreday of the hydrochloric acid period, and may, therefore, be regarded as better serving the purpose of basal data with which to compare the alteration in values caused by ammonium chlorid ingestion. The data from the ammonium chlorid period cannot, however, be regarded as so satisfactory as those representing the effect of hydrochloric acid ingestion, because of this lack of a sufficiently long fore period on the diet used and the consequent uncertainty of stationary retention values, aside from the effect on these values of the ingested ammonium chlorid. Moreover, the collections in two instances (the first and the fourth day specimens) were incomplete during this period. This fault was roughly repaired by estimating the twenty-four hour values in these specimens on a basis of interpolated values for creatinin excretion. So far as the data are used to show the manner of acid-base excretion, it is believed that this illustrative purpose is not seriously interfered with by the lack of absolute accuracy in the values given. The values given in Tables 4 and 5 are arranged according to the plan indicated in Table 3. The data given in the tables are reproduced graphically in Figures 1 and 2. In these charts the diagram on the left

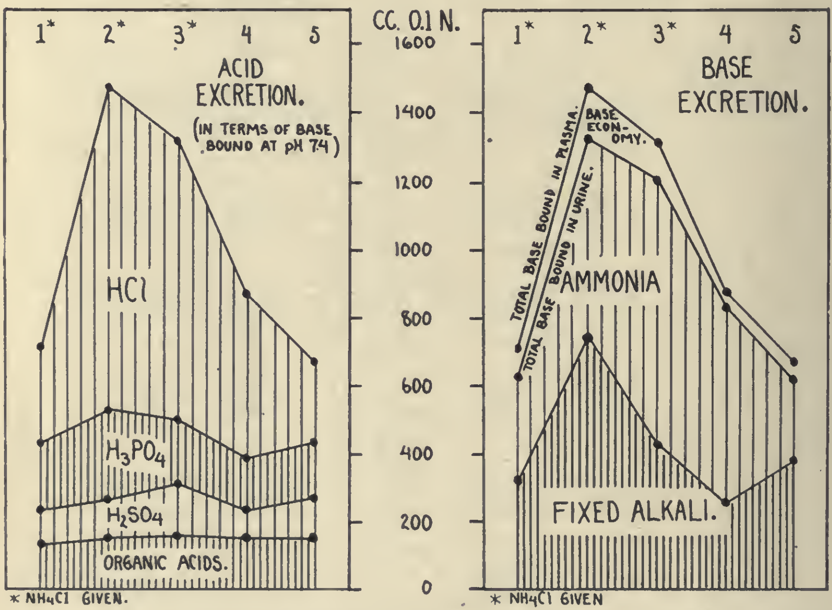


Fig. 1.—Acid and base excretion following ingestion of ammonium chlorid; diagrams constructed from data in Table 4.

represents the acid excretion. The values for the individual acids being superimposed, the top line measures, from the base line, the total acid excretion. The manner in which base is used in the elimination of this total acid excretion is indicated by the diagram on the right. The top line in this diagram is transferred from the diagram on the left; i. e., it measures from the base line the base bound by the total acid excretion while being carried for excretion. Laying off downward from the points on this line the measurements of the titratable acidity of the urine, "base economy" is indicated and a line obtained which measures from the base line the total of base carried into the urine. Laying off again the measurements of ammonia in the urine, the remainder of the distance to the base line measures the fixed alkali excretion. These diagrams, it is believed, will serve to illustrate rather more clearly than the data in Tables 4 and 5 the operation of the factors which control the extent to which fixed alkali is used in the process of acid excretion. The large need for regulation of fixed alkali excretion is indicated by the fact that the total acid excretion was doubled by the amounts of ammonium chlorid and of hydrochloric acid given. The much greater size of the ammonia factor is apparent. The "base economy" factor is not, except under circumstances producing large increase in the excretion of phosphoric acid or of organic acids, widely extensible. We have noted, however, from other data, that on usual diets its value,

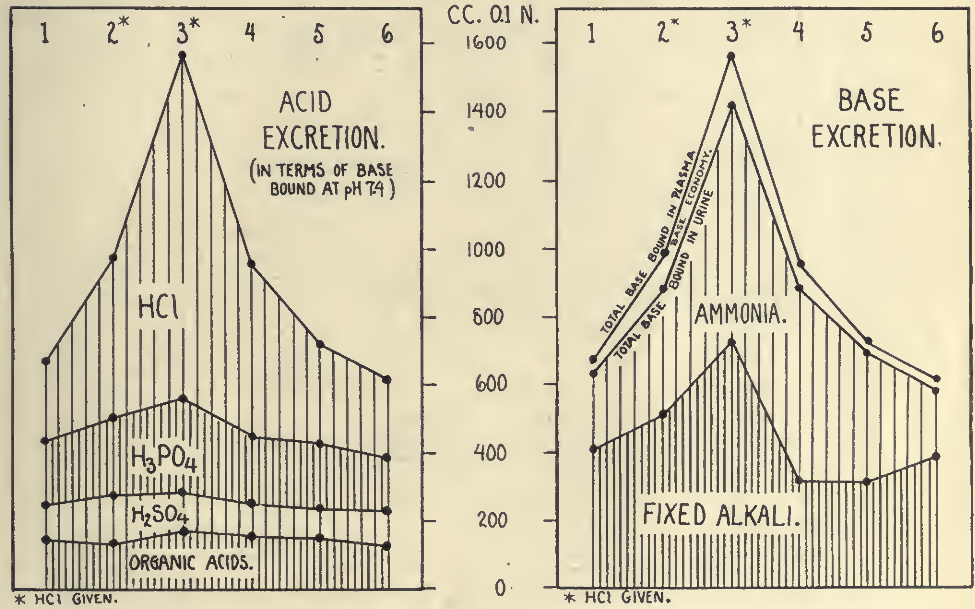


Fig. 2.—Acid and base excretion following ingestion of hydrochloric acid; diagrams constructed from data in Table 5.

as might be expected, is considerably more variable from day to day than the ammonia excretion, and we venture the conjecture that this factor may be regarded as the "fine adjustment" of the mechanism regulating fixed alkali excretion.

The data from the ammonium chlorid period of the experiment serves, as well as those obtained following hydrochloric acid administration, the purpose of illustrating the operation of the factors controlling fixed alkali excretion. Presumably, regardless of the extent to which ammonia is ingested, it will enter the urine to an extent regulated according to the need for conservation of fixed alkali. The regulated use of ammonia following ingestion of ammonium chlorid is quite apparent when the amounts of ammonia and of chlorin estimated, as derived from the ingested ammonium chlorid, are compared. To present this comparison the diagrams in Figure 3 were constructed. The values there charted represent the increase in the urine of ammonia and of chlorin following the ingestion of ammonium chlorid. They were obtained by subtracting from the total values for the days indicated the values found in the urine collected during the second day following cessation of ammonium chlorid administration. Inspection of the

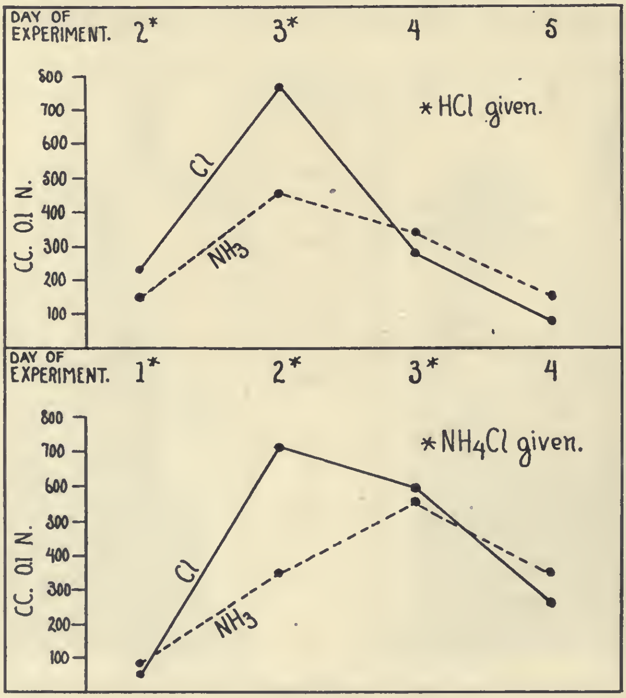


Fig. 3.—Increase in excretion of chlorin and of ammonia in urine during hydrochloric acid and ammonium chlorid periods.

diagram will make clearly evident the fact that the excretion of ammonia and of chlorin from ingested ammonium chlorid are separately controlled. Chlorin is seen to enter the urine more rapidly than ammonia. The figure also contains a diagram representing the increase in chlorin and ammonia in the urine following the administration of hydrochloric acid. The curves obtained are of quite the same character as those of the ammonium chlorid period, and the inference is that, at least from the point of view of the process of acid excretion, the ingested ammonium chlorid may be regarded as hydrochloric acid. More precise evidence in support of this surmise may be obtained by noting the ratio of ammonia to chlorin in the urine in both periods, using total values for the two days of hydrochloric acid administration and, for the first two days of the three day ammonium chlorid period. The data obtained from Tables 4 and 5 are these:

Ammonium chlorid period: ammonia, 878 c.c. tenth normal; chlorid (Cl^-), 1,223 c.c. tenth normal; $\frac{NH_3}{Cl} = 0.72$.

Hydrochloric acid period; ammonia, 1,063 c.c. tenth normal; chlorid (Cl^-), 1,470 c.c. tenth normal; $\frac{NH_3}{Cl} = 0.72$.

The absolute agreement of the ammonia to chlorid ($\frac{NH_3}{Cl}$) ratio is striking and would seem to permit with certainty the inference that the effect of administering ammonium chlorid is, from the point of view of acid excretion, the same as would be obtained from placing its equivalence as hydrochloric acid in the milk.

3. THE MANNER OF THE EFFECT OF AN INCREASED METABOLISM OF HYDROCHLORIC ACID ON THE EXCRETION IN THE URINE OF OTHER ACID SUBSTANCES AND OF FIXED ALKALI

The manner of the control of fixed alkali excretion is fairly completely indicated by the data in Tables 4 and 5 and by means of Figures 1 and 2. It is evident, however, from these tables and figures that following the ingestion of ammonium chlorid and of hydrochloric acid there occurs a large increase in the excretion of fixed alkali. Since the data from the hydrochloric acid period of the experiment (Table 5) are more complete and of a better degree of accuracy than those representing the effect of ammonium chlorid ingestion, they will be used as a basis for consideration of the probable significance of the increased excretion of fixed alkali. An estimation of the size of the increase in fixed alkali excretion may be arrived at by comparing the amount of fixed alkali eliminated when hydrochloric acid was given with the amount found in the urine collected during the foreday. Thus, the fixed alkali excretion during the two days of hydrochloric acid administration was (Table 5) 504 plus 732 = 1,236 c.c. tenth normal. For the foreday this value was 407 c.c. tenth normal. Regarding this as a stationary value for the diet used, the excretion for two days should be

814 c.c. tenth normal, and the increase when hydrochloric acid was given may be taken as 1,236—814 = 422 c.c. tenth normal, approximately a 50 per cent. increase. It may also be deduced from the data in Table 5 that immediately following cessation of hydrochloric acid ingestion, the inorganic base excretion fell below its foreday value to the extent of 89 plus 92 plus 21 = 202 c.c. tenth normal, for the three days that it was measured, indicating a recovery during this period of about one half of the base lost during hydrochloric acid administration.

It may also be seen in Table 5 and in Figure 2 that when hydrochloric acid is given there occurs an increase in the excretion of the other three urinary acids. During the foreday the excretion of organic acids plus sulphuric acid plus phosphoric acid amounted to 437 c.c. tenth normal. For each of the two days when hydrochloric acid was given, the sum of these acids was 505 and 565 c.c. tenth normal, respectively. The increase in excretion of acids other than hydrochloric acid may, therefore, be taken as 68 plus 128 = 196 c.c. tenth normal. Of this increase it may be estimated, from the data in Table 5, that 128 c.c. tenth normal is due to increase in the excretion of phosphoric acid.

There is thus presented for consideration the fact that an increase in the metabolism of hydrochloric acid has caused an increase in the excretion of fixed alkali and also an increase in the excretion of urinary acids (other than hydrochloric acid), especially of phosphoric acid. In explanation of this fact in general terms, a choice between two hypotheses is indicated.

1. An increase in metabolism of hydrochloric acid brings about a withdrawal of fixed alkali from the body fluids, presumably in consequence of the unusual size of the acid excretion, and also in a manner quite obscure causes withdrawal from the body fluids of other acid substances. If this is the case the effect of hydrochloric acid administration is to reduce base concentrations within the body and also concentrations of acid substances, especially that of phosphoric acid (as phosphates).

2. The alternative explanation assumes that the unusual size of the chlorid excretion has produced a withdrawal of body water. In proportion to the reduction of the volume of body fluids an increased amount of base will obviously become available for use in the process of acid excretion without reduction of base concentrations. As regards the possibility of a reduction of the volume of body fluids causing an increase in the excretion of acid substances may be noted the huge concentration of chlorid (Cl^-) in the blood plasma and (according to the data of Katz[8]) a probably considerable concentration of phosphates in the water of muscle tissue.

From these two hypotheses widely different inferences as regards the effect of hydrochloric acid ingestion on acid-base values in the body fluids are to be obtained. Base concentrations, for instance, are either considered to be reduced in consequence of an excessive base excretion or are believed to be correctly sustained, the extra fixed alkali in the urine being explained as derived from lost body water. It is, indeed, quite impossible to proceed in a consideration of the effects of hydrochloric acid ingestion without first coming to a decision as to the probable cause of the increased excretion of fixed alkali and of acid substances. We wish to present here an interpretation of the data at hand favoring the view that the extra fixed alkali in the urine and the increased excretion of acid substances are caused by a loss of body fluids. Assuming a reduction in the volume of body fluids, we will expect an increase in chlorid (Cl^-) excretion apart from the increase due directly to chlorid (Cl^-) added to the intake. The chlorid (Cl^-) contained in the lost body water may, without affecting base concentrations, carry into the urine the fixed alkali which it bound in the body fluids. This portion of the chlorid (Cl^-) excretion should, therefore, exert no demand for extension of the base saving factors (titratable acidity and ammonia). It may, therefore, be undertaken to measure the part of the chlorid (Cl^-) excretion due to loss of body water by comparing the extension of the base saving factors with the increase in chlorid (Cl^-) elimination. For the two days of hydrochloric acid administration the increase in titratable acidity plus ammonia is found from the data in Table 5 to be 778 c.c. tenth normal. The increase in hydrochloric acid excretion for these two days is 1,004 c.c. tenth normal. It is thus seen that 226 c.c. tenth normal of the increase in hydrochloric acid excretion is not covered by extension of the base saving factors and may, on the basis of an assumption of a loss of body water, be explained as chlorid (Cl^-) entering the urine along with the fixed alkali which carried it within the body. Justification for applying the extension of the base saving factors entirely to the excretion of the ingested hydrochloric acid is contained in the conception that the increased excretion of the other acid substances, being also a consequence of a loss of body water, permits their carrying with them the inorganic base which they bound in the body fluids. It was noted above that the estimated increase in the fixed alkali excretion during the two days of hydrochloric acid administration was 422 c.c. tenth normal and that the increase in the urinary acids other than hydrochloric acid was 196 c.c. tenth normal. Assuming that the increase in fixed alkali excretion was a consequence of a reduction of the volume of body fluids, we obtain again $422-196=226$ c.c. tenth normal as the portion of the increased chlorid (Cl^-) excretion due to the same cause. Regarding the loss of body water as due to a large increase in the metabolism of hydrochloric acid, the fact that chlorid (Cl^-) is carried chiefly in extracellular body water, blood plasma, for example, suggests that the loss of water will occur chiefly at the expense of extracellular fluids. In blood plasma 66 per cent. of the inorganic base is bound by chlorid (Cl^-). In approximate agreement with this value the 226 c.c. tenth normal chlorid (Cl^-) assumed to be derived from lost body water is 54 per cent. of the equivalence of the increase in inorganic base excretion (422 c.c. tenth normal), which is being regarded as from the same source. In further defense of the conception of a reduction of the volume of body water as a reasonable means of explaining the facts at hand, it may be noted that, in contrast to the alternative view, it accounts for the increase in the excretion of acids as well as of base, and it credits the kidney with being able to maintain a correct control of acid-base excretion. To our minds, it is much more in accord with the known principles of acid-base excretion.

The assumption of a loss of body water is supported by the fact that a large increase in the volume of urine occurred when hydrochloric acid was given (Table 5), the urine volume for the foreday being 440 c.c. and for each of the two days of hydrochloric acid administration, 650 and 790 c.c., respectively.[13] Regrettably the infant was not weighed directly before and following the hydrochloric acid period. A large loss of body weight during the three days of ammonium chlorid administration, 540 gm., was, however, measured and constitutes emphatic evidence of a loss of body water.

Table 6.—*Concentration of Sodium in Blood Serum After Administration of Ammonium Chlorid, Calcium Chlorid and Hydrochloric Acid*

	Na Mg. per 100 C.c.
NH_4Cl given for two days	333
Two days after discontinuing NH_4Cl	326
$CaCl_2$ given for two days	320
HCl given for two days	327

The concentration of base in the blood serum of this subject was not completely measured, although a few determinations of sodium were made. Since sodium constitutes 92 per cent. of the base in blood serum, the size of the total base concentration may be assumed to be fairly closely indicated by a measurement of sodium alone. The values found are given in Table 6, and it may be seen that they approximate very closely the average usual value, 330 mg. per hundred cubic centimeters of serum. The fact that the concentration of this chief base in the blood serum was not found to be measurably reduced in the presence of the large increase in the excretion of fixed alkali occurring during the first two days of ammonium chlorid and of hydrochloric acid administration makes the inference permissible that the regulation of inorganic base excretion was closely correct. In the preceding paper, we[1] noted that the total base concentration, measured by determining separately the amounts of sodium, potassium, calcium and magnesium present, was not appreciably altered by the administration of calcium chlorid, although there occurred just preceding the measurements of base in the serum a large increase in the excretion of fixed alkali in the urine.

---

[13] Throughout the entire period of whole milk feeding the stools were formed and unusually dry. There was, therefore, no appreciable variation of water loss by way of the bowel. The stools were collected the day before and the first day following hydrochloric acid administration and their chlorin content was determined. The very small amounts found, 13 c.c. tenth normal and 6 c.c. tenth normal for each twenty-four hours, respectively, are negligible in relation to the measurements of hydrochloric acid metabolism obtained from the urine.

It is, we believe, the evidence of these data that the increased excretion of acids and fixed alkali in the urine following an increase in the metabolism of hydrochloric acid may best be explained as at least chiefly a consequence of a loss of body water and probably not, to an appreciable extent, derived at the expense of concentrations in the body fluids. These data are not, however, of a precision to prove that a slight loss from concentrations within the body does not occur.

Scheer[5] noted the increased phosphoric acid elimination in the urine following administration of "hydrochloric acid milk." By means of measurements of phosphorus in the stools, he was able to show that the increase in the urine was largely a consequence of an increased absorption. Hydrochloric acid may as Scheer points out, very reasonably be assumed to promote absorption of phosphates. Such an effect would not, however, be expected from ingestion of ammonium chlorid. György[14] has demonstrated quite thoroughly that an increase in phosphate elimination follows ammonium chlorid administration. He has inferred from this fact a lag in the intermediary metabolism of phosphoric acid in tetany which is in some way corrected by the large increase in acid metabolism following the ingestion of ammonium chlorid. We do not wish to deny that this may be the case. We prefer, however, the less elaborate and, to our minds, much more probable conception that the increased phosphate excretion is due simply to a reduction of the volume of the body fluids caused by the diuretic action of ammonium chlorid.

4. THE MANNER OF THE EFFECT OF AN INCREASED METABOLISM OF HYDROCHLORIC ACID ON THE PLASMA BICARBONATE

The fact that the bicarbonate of the blood plasma may be lowered by the ingestion of ammonium chlorid was demonstrated by Haldane.[4] Scheer[5] measured a considerable reduction of the bicarbonate of the plasma of infants with tetany while receiving "hydrochloric acid milk." With F. F. Tisdall,[1] we found a decrease in the plasma bicarbonate following the administration of calcium chlorid to infants and were, moreover, able to demonstrate that the lowering of bicarbonate was due in large part, perhaps entirely, to increase in the chlorid concentration. The total base concentration in the serum was not found to be measurably reduced. The reduction of bicarbonate could not, therefore, be due, to an appreciable extent, to a withdrawal of base from the plasma. We have given above evidence indicating that, although a large increase in fixed alkali excretion occurs following the administration of ammonium chlorid or of hydrochloric acid (as was also found to occur following the ingestion of calcium chlorid), the total concentration of base in blood serum is not appreciably diminished, presumably because of a loss of water corresponding to the increased excretion of fixed alkali. Coinciding with this view, the measurements of bicarbonate and of chlorid in the serum given in Table 7 show an approximately equivalent inverse alteration following the administration of ammonium chlorid or of hydrochloric acid which precludes the necessity of assuming a decrease in base in explanation of the lowering of bicarbonate. The table also includes measurements representing the effect of calcium chlorid ingestion. The amounts of bicarbonate and of chlorid found are expressed in the usual terms, percentage by volume of bound carbon dioxid and grams of sodium chlorid per liter, respectively, and also, in order to compare the extent of their alterations in equivalent terms, as cubic centimeters of tenth normal base bound per hundred cubic centimeters of serum. A large decrease in bicarbonate accompanied by an increase in chlorids may be seen following the administration of ammonium chlorid, calcium chlorid or hydrochloric acid. The approximately stationary value for the sum of the concentrations of chlorid (Cl^-) and bicarbonate (HCO_3^-) in terms of base bound given in the

---

[14] György, P.: Jahrb. f. Kinderh. **99**:104 (Aug.) 1922.

TABLE 7.—*Concentration of Bicarbonate and of Chlorids in Blood Serum Before and Following Administration of Ammonium Chlorid, Calcium Chlorid and of Hydrochloric Acid*

Date		$BHCO_3$		BCl		$BHCO_3$ + BCl
		Per Cent. by Volume of Carbon Dioxid	C.c. Tenth Normal per 100 C.c.	Gm. NaCl per 1,000 C.c.	C.c. Tenth Normal per 100 C.c.	C.c. Tenth Normal per 100 C.c.
May 6	Before giving NH_4Cl	57.0	25	6.07	105	130
8	NH_4Cl given for 2 days	29.6	13	7.00	121	134
9	NH_4Cl given for 3 days	37.2	17	6.67	115	132
11	NH_4Cl discontinued for 2 days	57.9	26	6.00	104	130
May 13	$CaCl_2$ given for 2 days	31.9	14	6.67	115	129
16	$CaCl_2$ discontinued for 2 days	54.1	24	5.93	102	126
June 5	Before giving HCl	52.3	23	6.07	105	128
7	HCl given for 2 days	31.9	14	6.87	119	133
10	HCl discontinued for 3 days	44.9	20	6.13	106	126

last column of the table brings out clearly their closely inverse relationship and is also evidence that the usual amount of base in the serum for the binding of chlorid ($\mathrm{Cl^-}$) plus bicarbonate ($\mathrm{HCO_3^-}$) has not been appreciably altered. Further illustration of this point is provided by the diagram in Figure 4. The concentrations of chlorid ($\mathrm{Cl^-}$) and of bicarbonate ($\mathrm{HCO_3^-}$) in terms of base bound per hundred cubic centimeters of serum are here superimposed. The lower of the dotted lines across the chart represents the usual average concentration of $B\mathrm{Cl}$, and the upper dotted line, the amount of base bound by the sum of the average concentrations of chlorid ($\mathrm{Cl^-}$) and bicarbonate ($\mathrm{HCO_3^-}$), the intervening space thus representing the usual concentration of $B\mathrm{HCO_3}$. It will be seen that the amount of base bound by chlorid ($\mathrm{Cl^-}$) plus bicarbonate ($\mathrm{HCO_3^-}$) remains a nearly stationary value, so that with increase in $B\mathrm{Cl}$ there occurs, necessarily, reduction of $B\mathrm{HCO_3}$. With disappearance of the excessive $B\mathrm{Cl}$ concentration, $B\mathrm{HCO_3}$ resumes its usual size. The diagram makes quite clear the fact that the decrease in bicarbonate following ingestion of ammonium chlorid, calcium chlorid or hydrochloric acid is, for the most part, perhaps entirely, to be explained by an increase in chlorid at the expense of bicarbonate and is not to an appreciable extent caused by reduction of the absolute amount of base in the serum. There is, indeed, in the diagram a suggestion of a slight increase in the amount of base bound

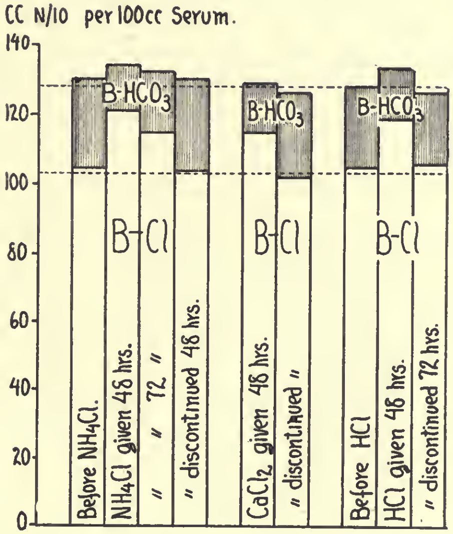


Fig. 4.—Close relationship of the bicarbonate lowering and chlorid increase following administration of ammonium chlorid, calcium chlorid and hydrochloric acid. The measurements obtained, given as cubic centimeters tenth normal per hundred cubic centimeters of serum, are superimposed in the diagrams.

by chlorid (Cl^-) plus bicarbonate (HCO_3^-). As the appreciable rise in this value may be seen following ingestion of each of the substances used, it is probably not a product of error in the two measurements. It may be explained by assuming a slight shift of reaction in the direction of acidity. This would cause a small reduction in the amount of base bound by phosphoric acid and protein with equivalent increase in base available for binding carbonic acid.

An interesting significance of these data is the apparently specific manner of the reduction of bicarbonate following the ingestion of hydrochloric acid or of hydrochloric acid producing substances. The lowered bicarbonate is probably not simply a consequence of ingestion of an unusual amount of unoxidizable acid. It is doubtless closely related to the fact that chlorin, as compared with other acid ions in the plasma, is held at a huge concentration, covering, when of usual average size, three fifths of the base in the plasma. An unusual demand for the transport of chlorin entering the body fluids without an equivalent of base may be expected to increase the chlorin concentration to an extent which, though not large in relation to the usual concentration, will greatly alter the amount of base available for binding carbonic acid.

5. THE REACTION OF THE BLOOD PLASMA IN THE PRESENCE OF AN INCREASED METABOLISM OF HYDROCHLORIC ACID

Demonstration of a reduction of bicarbonate in the plasma does not constitute evidence of a shift of its reaction in the direction of acidity. The reaction of the plasma may be said to be chiefly determined by the ratio of free to bound carbonic acid. The concentration of free carbonic acid in the plasma is determined by the tension of carbon dioxid in the alveolar air spaces, and the latter value is under control of the respiratory mechanism. A large reduction of the carbon dioxid tension in the alveolar air spaces may, for instance, be brought about by the simple maneuver of greatly increasing the volume of lung ventilation (hyperpnea). With reduction of the carbon dioxid tension in the alveolar air, the concentration of free carbonic acid in the plasma will fall correspondingly. The respiratory mechanism is thus potentially able to compensate over a wide range for a reduced bicarbonate by effecting a decrease in the free carbonic acid of the plasma of such extent that the usual $H_2CO_4 : BHCO_3$ ratio (1:20) will be maintained and a change in reaction of the plasma avoided.

It is usually assumed that all except excessive reductions of the plasma bicarbonate from any cause are compensated for, through the agency of the respiratory center, to such an extent as to prevent an appreciable alteration in the reaction of the plasma. Such a generalization is probably incorrect. Regarding the blood as a physicochemical mechanism, the quite absolute interdependence of its structural parts has been illustrated and emphasized by L. J. Henderson.[15] It is, therefore, probably not permissable to postulate a stationary reaction of the plasma on the basis of a potential ability of the respiratory center to provide it. It is, for instance, conceivable that certain alterations in the structure of this mechanism would make necessary its operation at a p_H differing from the usual one.

It was, therefore, desirable to measure directly the p_H of the serum in the presence of a lowered bicarbonate brought about in a particular manner by the increase in hydrochloric acid metabolism. For this purpose the recently devised colorimetric method of Cullen was used. Unfortunately we became equipped for this method only before the last (hydrochloric acid) period of the experiment. The measurements of p_H of the blood serum obtained during this period were as follows: before giving hydrochloric acid, 7.39; after giving hydrochloric acid for two days, 7.22, and after hydrochloric acid was discontinued for three days, 7.34. Their significance should be considered with the circumspection required by the fact that they constitute a single set of observations. It must also be said regarding them that the standards used, although carefully prepared according to Cullen's specifications, were not electrometrically tested. The measurements cannot, therefore, be warranted as regards their absolute values. They may, however, be taken as dependably demonstrating and approximately measuring a change of reaction in the direction of acidity in the blood serum of this subject following ingestion of hydrochloric acid. We do not wish to offer conjecture as to the cause of so considerable a change of reaction following a reduction of bicarbonate of a degree presumably well within the range of compensation by respiratory adjustment.

It may be noted that demonstration of an actual change of reaction supports the explanation of the small contribution to the base available for binding bicarbonate noted in the preceding section.

The outcome of these p_H measurements in the serum following hydrochloric acid ingestion indicates the possibility that an increase in hydrogen ion concentration may also be a factor in the therapeutic action of these hydrochloric acid producing substances.

6. THE PROBABLE THERAPEUTIC SIGNIFICANCE IN TETANY OF REDUCTION OF BICARBONATE AND INCREASE IN HYDROGEN ION CONCENTRATION IN THE BLOOD SERUM

Physiologists have shown that each of the bases found in the body fluids exerts an effect on neuromuscular excitability, that of sodium and potassium being augmentative in contrast to a depressant action by calcium and by magnesium. It is probable that the normal degree of excitability of the neuromuscular mechanisms is the result of a correct balance in these antagonistic effects and is maintained by reason of closely stationary values for the separate concentrations of the four bases in the body fluids. Howland and Marriott [2] have demonstrated that the calcium concentration is a strikingly constant value in blood serum of infants, except in the case of infants manifesting symptoms of active tetany. The serum from infants with tetany is found to contain greatly less, often only half as much, calcium as the serum of normal infants or infants suffering from other ailments than tetany. The data derived from Katz' analyses given in Table 2 indicate approximately the same concentration of calcium in the water of muscle tissue as in the water of blood serum and permit the surmise that the intracellular and extracellular concentrations of calcium will vary together. Evidence of appreciable alterations in infantile tetany of the usual concentrations of the other three bases, at least in blood serum, has not been found. For instance, the few measurements of sodium, the chief base in the serum, given above, are close to the average value. Owing to the deficiency of calcium in tetany, demonstrable in the blood serum and probably extending throughout the body fluids, the normal balance of the antagonistic effects of the bases may be assumed to be altered in a direction lowering the threshold of neuromuscular excitation.

---

[15] Henderson, L. J.: J. Biol. Chem. **46**:411 (April) 1921.

The low calcium content of the serum found in infantile tetany would thus seem clearly to be indicated as the cause of the increased neuromuscular irritability. We wish now to consider the probable manner of a therapeutic effect from lowering of the bicarbonate or increase of the hydrogen ion concentration of the serum. As indication of a relationship of the size of the bicarbonate concentration and of the degree of acidity of the plasma to the state of excitability of the neuromuscular mechanism, it may be cited that in gastric tetany the bicarbonate concentration is greatly increased,[16] and, in the experimental tetany produced by overbreathing, the reaction of the plasma shifts in the direction of alkalinity,[17] and that in both of these types of tetany the calcium concentration of the serum is not diminished. We are indebted to Freudenberg and György [18] for pointing out the usefulness of the results of a study by Rona and Takahaski [19] of the factors determining the solubility of calcium carbonate in blood serum as a means of explaining the manner in which the bicarbonate concentration and the reaction of the serum may be concerned in the presence or in the disappearance of the symptoms of tetany. The significance of the degree of solubility of calcium carbonate in blood serum is that only that part of the total calcium present in serum which is in true solution (as calcium carbonate) can be regarded as capable of providing ionized calcium. Presumably, calcium exerts its physiologic effect only to such extent as physicochemical conditions permit its presence as ionized calcium. Rona and Takahaski derived on theoretical grounds the following simple equation to express the dependence of the degree of ionization of calcium in blood serum on the size of the concentrations of bicarbonate and of hydrogen ions: $\frac{(Ca^{++})\ (HCO_3^-)}{(H^+)} = \text{Constant}$, and were able to establish it by direct measurements of the solubility of calcium carbonate (determined by measuring calcium) in solutions containing various amounts of bicarbonate and of differing degrees of reaction. The formula when applied to these measurements was found to give a closely constant value. If the significance of these results is correctly transferable to blood plasma, the extent to which ionized calcium may be present in the plasma may be taken to be determined by the size of the bicarbonate and of the hydrogen ion concentrations. According to the formula, increase in bicarbonate will diminish ionized calcium, whereas increase in hydrogen ion concentration will permit a larger concentration of ionized calcium.

---

[16] McCann, W. S.: J. Biol. Chem. **35**:553 (Sept.) 1918; McCallum, W. G., Lintz, J., Vermilye, H. N., Leggett, T. H., and Boas, E.: Bull. Johns Hopkins Hosp. **31**:1 (Jan.) 1920; Hastings, H. B., Murray, C. D., and Murray, H. A.: J. Biol. Chem. **46**:223 (March) 1921.

[17] Collip, J. B., and Backus, P. L.: Am. J. Physiol. **51**:568 (April) 1920; Grant, S. B., and Goldman, A.: Am. J. Physiol. **52**:209 (June) 1920.

[18] Freudenberg, E., and György, P.: Jahrb. f. Kinderh. **96**:5, 1921.

[19] Rona, P., and Takahaski, D.: Biochem. Zitschr. **49**:370, 1913.

By means of the following modification by Michaelis [20] of Rona and Takahaski's formula the amount of ionized calcium which should be present in blood plasma at given bicarbonate and hydrogen-ion concentrations may easily be calculated;

$$(Ca) = 340 \times \frac{(H)}{(HCO_3)} \text{ mol per liter}$$

Taking the normal p_H of the plasma (of venous blood) as 7.25 [21] and the bicarbonate as 55 per cent. by volume, and using the molar equivalents of these values [22] in the formula, the calculated amount of ionized calcium is approximately 3 mg. of calcium per hundred cubic centimeters; i. e., about one third of the total calcium normally present. In tetany the reduction of total calcium is rarely below 5 mg. per hundred cubic centimeters of plasma, and there is, therefore, present enough calcium to provide 3 mg. of ionized calcium (Ca^{++}), assuming hydrogen ion (H^+) and bicarbonate ion in (HCO_3^-) concentrations are of usual size and that there is no interference with the operation of these factors in determining the concentration of calcium ions (Ca^{++}) in the manner indicated by the foregoing formula. Evidently, however, the reduction of total calcium does in some way interfere with the ionization of calcium to a usual extent. Conceivably, however, the lowered calcium ion concentration in tetany may be raised to its usual value, without increasing the total calcium by sufficiently altering the two factors, hydrogen ion and bicarbonate ion concentrations, in a manner favoring the ionization of calcium. A marked lowering of the plasma bicarbonate has been demonstrated above, following the administration of hydrochloric acid producing substances, and following the ingestion of hydrochloric acid, a very considerable increase in hydrogen ion concentration. These alterations of bicarbonate ion and hydrogen ion concentrations are in the direction which, according to Rona and Takahaski's formula, should increase the ionization of calcium, and it may, therefore, very reasonably be concluded that these changes are directly effective in causing the disappearance of the symptoms of tetany.

---

[20] Michaelis, L.: Die Wasserstoffionen-Konzentration, Berlin, **1**:71, 1922.

[21] It will be noted that the average usual reaction of the plasma is here taken as p_H 7.25, whereas in the preceding section dealing with the process of acid excretion a plasma p_H of 7.4 was assumed. This discrepancy is regretted. The older value, p_H 7.4, was used in titrating the urines as a result of habit. Recent evidence has indicated that the normal reaction of the plasma is probably more accurately taken as p_H 7.25. The measurements of "base economy" in the excretion of acid in the urine given in the preceding section, may, therefore, be regarded as a trifle larger than they should be.

[22] The concentration of bicarbonate (HCO_3^-) should, according to Michaelis, be multiplied by 0.9 to allow for undissociated $BHCO_3$.

The manner in which a reduction of total calcium causes a lowering of ionized calcium is not clear. In order to discuss this point the forms in which calcium is carried in the plasma may be briefly described. As has been mentioned, the concentration of ionized calcium calculated by means of Rona and Takahaski's formula is approximately one third of the usual total calcium content. This theoretical value has recently been confirmed by direct measurements of the ionized calcium in the plasma, made by Brinkman and Van Dam.[23] It is the evidence of dialysis experiments that approximately another one third of the usual total calcium is bound by protein.[19] The character of the remaining one third of the plasma calcium has not been satisfactorily explained. Rona and Takahaski [19] have conjectured that this fraction of the total calcium is held as calcium carbonate in excess of the limits of a true solution of this salt as determined by the physicochemical factors in the plasma. The calcium thus held as calcium carbonate in supersaturated solution is assumed to be nondissociable. If this admittedly somewhat difficult conception is correct, the surmise is permissible that a reduction of total calcium in the plasma would be at the expense of calcium held in supersaturated solution, and should not, unless very extensive, cause a lowering of the concentration of ionized calcium. Another point which should be considered here is the possibility that the decrease of ionized calcium in tetany may, at least in part, be due to a reduction of hydrogen ion concentration. The concentration of bicarbonate in the tetany of infants has been observed to be of a usual degree. We are not, however, satisfactorily informed as to the values which obtain for hydrogen ion concentration in untreated tetany. It is conceivable that the lowering of ionized calcium is largely a consequence of an abnormally low hydrogen ion concentration. It may be pointed out, however, that a very large decrease in hydrogen ion concentration would be necessary to cause a considerable reduction of ionized calcium. For instance, bicarbonate remaining at its usual value (55 per cent. by volume), it may be calculated by means of the foregoing formula that the p_H of the plasma would have to become 7.55 (probably near or past the physiologic limit of alkalinity) in order to depress the ionization of calcium below 2 mg. per hundred cubic centimeters. A measurement of the reaction of the plasma obtained from this infant before the administration of hydrochloric acid and while the child was manifesting symptoms of active tetany does not support the surmise that the lowered calcium ion concentration in tetany may be chiefly the result of an increased alkalinity of the plasma. The reaction of the plasma, in this single instance, was found to be p_H 7.39; i. e., only slightly more alkaline than usual. Using this measurement and that of the bicarbonate concentration obtained from the same sample, the value for ionized calcium, calculated by means of Michaelis' modification of Rona and Takahaski's formula, is 2.7 mg. per hundred cubic centimeters and is thus not appreciably below the usual value (3 mg. per hundred cubic centimeters). The fact that the infant presented symptoms of active tetany would seem clearly to indicate that the actual calcium ion concentration was less than the calculated value, and to make necessary the assumption that the lowered total calcium has in some way interfered with the operation of the hydrogen ion and bicarbonate ion concentrations in determining the ionization of calcium. The data in Table 8 are given to illustrate the probability that the lowered calcium ion

---

[23] Brinkman, R., and Van Dam, E.: Kon. Akademie van Wetenschappen te Amsterdam, Proceedings **22**:762, 1920.

TABLE 8.—*Calculated Values for Calcium Ion (Ca^{++}) During Hydrochloric Acid Period Using Michaelis Modification of Rona and Takahaski's Formula*

Date	Treatment	Tetany	Bicarbonate, Per Cent. by Volume of Carbon Dioxid	p_H	Calculated (Ca^{++}), Mg. per 100 C.c.	Total Calcium in Serum, Mg. per 100 C.c.	Calculated (Ca^{++}) × Total Calcium ÷ 10, Mg. per 100 C.c.
June 5	Before HCl..........	+	52.3	7.39	2.7	5.0	1.4
7	HCl given 2 days....	0	31.9	7.22	6.4	7.6	4.9
10	HCl disc. 3 days.....	+	44.9	7.34	3.3	5.6	1.8
Average normal values........		..	55.0	7.25	3.0	10.0	3.0

concentration in tetany is chiefly a consequence of the diminished total calcium. Measurements of p_H, bicarbonate and total calcium obtained before, during and following the hydrochloric acid administration are given. In rough attempt to evaluate the effect of the lowering of the total calcium in determining ionized calcium, the values for the calcium ion concentration, calculated by means of the formula, are multiplied by the fraction of the usual total calcium of the plasma (taken as 10 mg. per hundred cubic centimeters) which was found in the samples taken from this subject. The values thus obtained are given in the last column of the table, and it will be seen that they are better in accord with the fact that the infant was manifesting symptoms of active tetany when the first and third set of measurements were taken.

Regardless of the question as to whether the immediate cause of the low calcium ion concentration in tetany is a more than usually alkaline reaction of the plasma or a less than usual total calcium, the formula of Rona and Takahaski explains excellently the increase in ionized calcium following an increase in hydrogen ion concentration or a decrease in bicarbonate and makes understandable the manner of the therapeutic action of substances which increase the metabolism of hydrochloric acid with the consequence that the hydrogen ion concentration is increased and that of bicarbonate lowered.

SUMMARY AND CONCLUSIONS

From a study of the effects, as regards acid-base metabolism, of administering calcium chlorid, ammonium chlorid and hydrochloric acid to an infant with tetany, the following findings may be stated:

1. The plasma bicarbonate following the ingestion of each of these substances is greatly lowered.

2. The reduction of bicarbonate is a consequence of an increased metabolism of hydrochloric acid which causes an extension beyond the normal of the chlorid content of the plasma at the expense of bicarbonate. Total base in the plasma remains closely stationary. The lowered bicarbonate is, therefore, not to an appreciable extent due to a withdrawal of base from the plasma.

3. The administration of these hydrochloric acid producing substances also causes a considerable increase in the hydrogen ion concentration of the plasma. This effect was directly demonstrated only in the case of hydrochloric acid, but may reasonably be assumed for calcium chlorid and ammonium chlorid.

4. The metabolism of these substances leads to an increased excretion of phosphates and of fixed alkali in the urine. It cannot be correctly inferred that the concentrations of these substances in the

body fluids are lowered. Their increased excretion may be satisfactorily explained as a consequence of a reduction of the volume of body water due to the diuretic action of the ingested agents.

The administration of ammonium chlorid does not raise the lowered calcium content of the plasma found in tetany. The therapeutic action of this salt may be entirely referred to an increased metabolism of hydrochloric acid, which causes a lowering of bicarbonate and an increase in hydrogen-ion concentration in the plasma, both of which alterations operate to produce an increased ionization of calcium. In consequence, a physiologically adequate concentration of ionized calcium is obtained from a lowered total calcium content. The therapeutic action of calcium chlorid and hydrochloric acid in tetany is in this respect identical with that of ammonium chlorid; but, in addition, ingestion of these substances causes an increase in the total calcium of the plasma. There is thus theoretical ground for regarding calcium chlorid and hydrochloric acid as more efficient agents than ammonium chlorid in the treatment of tetany. A relationship of the reduction of the volume of body water which follows the ingestion of these substances to their therapeutic action is not apparent.

CHEMICAL METHCDS USED

The measurements of calcium and sodium in blood serum were obtained by the methods of Kramer and Tisdall,[24] and of calcium, sodium and potassium in the urine by the methods described by Tisdall and Kramer.[25] For chlorids in the serum a combination of Van Slyke's plan of precipitating the protein with picric acid and Volhard's thiocyanate titration was used, this procedure being essentially the same as that recently described by Myers and Short.[26] The same method was used for chlorids in the urine. The bicarbonate of the serum was determined by Van Slyke's method.[27] The p_H of the plasma was measured colorimetrically by the method recently devised by Cullen.[28] The p_H and titratable acidity of the urine were determined by the methods of Palmer and Henderson.[29] Urine phosphates (inorganic) were measured by Fiske's [30] method and urine sulphates (inorganic) were weighed as barium sulphate, according to the method of Folin. The total organic acid excretion in urine was measured by the titration procedure of Van Slyke and Palmer.[31] Ammonia was determined in the urine by the method of Folin and MacCallum [32] and urine nitrogen by the usual Kjeldahl method.

---

24. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **47**:475 (Aug.) 1921; ibid. **46**:467 (May) 1921.

25. Tisdall, F. F., and Kramer, B.: J. Biol. Chem. **48**:1 (Sept.) 1921.

26. Myers, V. C., and Short, J. J.: J. Biol. Chem. **44**:47, 1920.

27. Van Slyke, D. D.: J. Biol. Chem. **30**:347 (June) 1917.

28. Cullen, G. E.: J. Biol. Chem. **52**:501 (June) 1922.

29. Palmer, W. W., and Henderson, L. J.: Clinical Studies on Acid Base Equilibrium and the Nature of Acidosis, Arch. Int. Med. **12**:153 (Aug.) 1913.

30. Fiske, C. H.: J. Biol. Chem. **46**:285 (April) 1921.

31. Van Slyke, D. D., and Palmer, W. W.: J. Biol. Chem. **41**:567 (April) 1920.

32. Folin, O., and MacCallum, A. B.: J. Biol. Chem. **11**:523, 1912.

THE EFFECT OF THE SPRAY PROCESS OF DRYING ON THE VITAMIN C CONTENT OF MILK

A PRELIMINARY REPORT *

GEORGE W. CAVANAUGH, B.S., R. ADAMS DUTCHER, B.S., M.S., M.A.
AND
JAMES S. HALL
ITHACA, N. Y.

On account of the conflicting statements in the literature regarding the vitamin C content of dried milk products, and especially in view of definite statements regarding the effect of the spray process on vitamin C, a special investigation of this problem has been conducted.

This investigation was started in February, 1922. The method consisted in feeding young guinea-pigs a standard basal diet free from vitamin C. To this was added raw liquid milk or spray process powdered milk in varying amounts, these milk products being the only source of vitamin C in the diet.

The milk, both liquid and powdered, was shipped by express daily from the Merrell-Soule Powdered Milk Factory at Perry, N. Y. The milk, both raw and powdered, which was used in this experiment was taken from the mixed milk of 175 dairies representing 1,276 cows. The raw milk for feeding was drawn each day from a large vat. In order to prevent souring of the raw milk, it was cooled and shipped in sterilized vacuum bottles. The milk in the vat was pasteurized under conditions known to be favorable to the preservation of vitamin C and then reduced to powder. The powdered milk for feeding was drawn each day from this powder so that the raw milk and powdered milk came from the same lot of fresh milk. Unless this precaution is taken, a fair comparison between raw and powdered milk cannot be made, as the vitamin C content of different lots of fresh liquid milk has been found to vary considerably. The experiments on winter milk were kept separate from those on summer milk on account of a similar variation.

This difference between summer and winter milk was confirmed by the present experiment. The fact indicates that no reliable conclusions regarding the effect of drying processes on the vitamin C content of milk can be drawn unless comparison is made between the dried

---

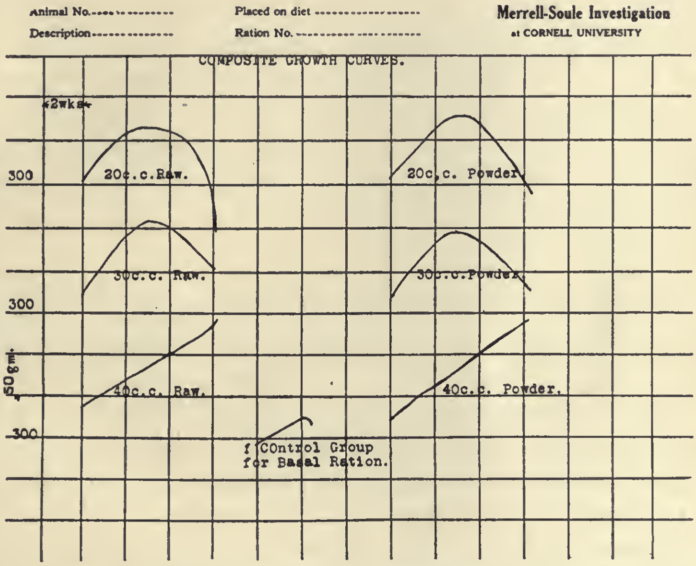
* Received for publication April 14, 1923.

* This investigation was carried on at the New York State College of Agriculture at Cornell University by George W. Cavanaugh, Professor of Agricultural Chemistry of Cornell University, and James S. Hall, under the direction and advice of Prof. R. Adams Dutcher, Head of the Department of Chemical Agriculture of the Pennsylvania State College.

milk and fresh raw milk taken from the *same* lot. Failure to take this precaution may probably account for some of the contradictory reports previously published.

PLAN OF EXPERIMENT

The guinea-pigs were arranged in groups according to the amount of milk fed, with eight or nine animals in each group. Each animal received, daily, the basal ration plus the milk to be tested, some groups receiving raw milk, others equivalent amounts of the powdered milk. The powdered milk was redissolved in water before being measured out for feeding, thus restoring it to the same water content as that of the raw milk.



Curves showing average growth of guinea-pigs in the six experimental groups and in the control group.

Careful records were kept for each animal showing daily basal ration intake, daily milk intake and body weight; also, date of development of scurvy, date of recovery from scurvy or date of death, when these events occurred. In each case of death, a necropsy was performed. This part of the experiment, in which 350 animals were used, extended over a period of seven months.

A careful study of all the groups, taking into account length of life, rapidity of growth, time of onset of scurvy and other factors indicated that milk, powdered by this spray drying process, was not inferior in antiscorbutic properties to the original raw milk. In other words, the result did not show any evidence of the destruction of vitamin C in milk powder prepared by this process.

The results of this part of the work were complicated by an epidemic of influenza in the colony, so that many animals had to be eliminated. There was also a lack of uniformity in the behavior of the animals within each group, owing apparently to the poor physical condition of many of them when received. These animals were obtained from three or four different breeders, which may in part account for the lack of uniform condition.

The experiment was, therefore, repeated. Special precautions were taken to obviate the foregoing difficulties. These may be of interest because a marked improvement in the uniformity of the results within each group and a consequent decrease in the experimental error were obtained.

All the guinea-pigs for the repetition of the investigation were obtained from the same source. Young animals were chosen from mothers that had been kept under identical conditions. These young animals had received the same food since birth. Healthy guinea-pigs weighing from 210 to 280 gm. were selected. Each one was placed at the caviary in an individual cage with some green food. They were then transported by hand to Cornell University, reaching their destination within twelve hours.

There these guinea-pigs were kept under observation for three weeks, and those that failed to grow normally were discarded. During this preliminary feeding period they received the following diet: a basal ration consisting of 60 per cent. of ground oats; 15 per cent. of wheat bran; 15 per cent. of ground autoclaved alfalfa; 5 per cent. of casein; 1 per cent. of calcium carbonate; 1 per cent. of sodium chlorid, and 3 per cent. of butter fat. In addition to this basal ration, whole milk and green grass were fed ad libitum.

At the end of the three weeks' observation period, the animals that showed normal growth curves were divided into six groups. Each group consisted of ten animals. The animals in each group received the basal ration ad libitum. In addition, they were given different amounts of raw whole milk and reconstituted Klim brand Merrell-Soule powdered whole milk according to this plan: Group 1, 20 c.c. of raw whole milk; Group 2, 20 c.c. of reconstituted milk powder; Group 3, 30 c.c. of raw whole milk; Group 4, 30 c.c. of reconstituted milk powder; Group 5, 40 c.c. of raw whole milk, and Group 6, 40 c.c. of reconstituted milk powder.

A control group of five animals received the basal ration with water ad libitum. Previous studies on the antiscorbutic properties of milk have shown that 30 c.c. is about the minimum amount that will protect guinea-pigs from scurvy. For this reason, levels of 20, 30 and 40 c.c. of milk were used in this experiment.

RESULTS

December 26, the sixty-first day of the experiment, the results showed that the average number of days for the onset of scurvy in groups fed raw and powdered milk are closely comparable.

The data obtained are given in the accompanying table.

Only five guinea-pigs of Group 5 developed scurvy, four of which have recovered. Only three guinea-pigs in Group 6 developed scurvy, all of which have recovered.

For this reason, no average time of onset of scurvy is given for these groups.

It was noted that the basal ration was apparently adequate, as the animals gained weight even while developing scurvy. This seems to eliminate complications only too common in this type of experiment in which incomplete diets are used for basal rations.

Results in Groups Fed Raw and Powdered Milk

	Average Weight at Beginning, Gm.	Average Maximum Weight, Gm.	Average Gain, Gm.	Average Time for Onset of Scurvy, Days
Control group	296	319	23	14.8
Group 1—20 c.c. raw milk	308.9	362.2	53.3	18.4
Group 2—20 c.c. powdered milk	310.7	376.1	65.4	20.3
Group 3—30 c.c. raw milk	319.6	402.6	83.0	21.1
Group 4—30 c.c. powdered milk	317.1	395.2	78.1	22.8
Group 5—40 c.c. raw milk	338.7	434.0	95.6	
Group 6—40 c.c. powdered milk	326.1	444.0	118.0	

The present part of this experiment is now in its sixty-first day. It will be continued for a total period of at least ninety days. A preliminary report is made at this time because the results seem to be concordant and to confirm the earlier and more extended part of the work.

A study of the groups at this time shows that the control group developed scurvy more quickly than the groups fed raw or powdered milk. Each group fed powdered milk did at least as well as the group receiving an equivalent amount of raw milk. So far as we can judge from data obtained from these experiments with guinea-pigs, there appears to be no destruction of the antiscorbutic properties of milk when it is thus powdered. This confirms the conclusions drawn from our first experiment; i. e., that milk powdered by this form of spray process possesses as great antiscorbutic properties as the raw milk from which it was made.

CONCLUSIONS

The results of these experiments to date indicate quite clearly that the spray process of drying milk preserves in its original strength the vitamin C; i. e., the antiscorbutic properties of milk.

The experiment is being continued to determine the effect of aging on the vitamin C content of powdered milk. So far, results indicate that spray process powdered milk probably retains its antiscorbutic properties for many months. Should this point be confirmed by the final results, its importance will be obvious. Summer milk, notably rich in vitamin C, could be powdered, and this powder could be used for infant and child feeding in the winter months, at which time raw milk is notably deficient in this vitamin.

INDEX TO VOLUME 25

PAGE

Bakwin, H.: Oxygen therapy in premature babies with anoxemia....... 157
  Water content of infants' blood during periods of rapid increase in weight 406

Bartlett, F. H., and Wollstein, M.: Brain tumors in young children; clinical and pathologic study.. 257

Blood, chemical studies of blood of mother and fetus; M. G. Howe and M. H. Givens.. 63
  intraperitoneal transfusion with citrated blood; a clinical study; D. M. Siperstein 202
  intraperitoneal transfusion with citrated blood; an experimental study; D. M. Siperstein and J. M. Sansby.................................. 107
  review of literature on blood and blood diseases of infants and children for last 4 years; L. W. Hill.................................. 168
  transfusion through umbilical vein in hemorrhage of new-born; report of case; J. B. Sidbury.. 290
  water content of infants' blood during periods of rapid increase in weight; H. Bakwin.. 406

Book Reviews:
  Anomale Kinder; L. Scholz.. 338
  Kurzes Lehrbuch der Kinderkrankheiten; H. Lehndorff................. 338
  Pelidisi-Table; C. Pirquet.. 338
  Premature and Congenitally Diseased Infants; J. H. Hess............... 411
  Principles of Professor Pirquet's System of Nutrition; E. Nobel......... 338
  Syphilis of the Innocent; H. C. Solomon and M. H. Solomon............. 411

Boyd, G., and Robertson, B.: Toxemia of severe superficial burns in children 163

Brain cyst in infant; H. G. Jacobi.. 435
  tumors in young children; clinical and pathologic study; M. Wollstein and F. H. Bartlett.. 257

Brown, E. W., and Gordon, J. K.: Types of organism found in series of tuberculous children.. 234
  —Hill, L. W., and Hunt, E. F.: Bacteriology of urine in acute nephritis in children.. 198

Burns, toxemia of severe superficial burns in children; B. Robertson and G. Boyd.. 163

Calcium absorption in children on diet low in fat; L. E. Holt and H. L. Fales 247

Cavanaugh, G. W., Dutcher, R. A., and Hall, J. S.: Effect of spray process of drying on vitamin C content of milk.............................. 498

Celiac disease; R. Taylor.. 46

Cerebrospinal fluid in postdiphtheric paralysis, characteristics of; J. C. Regan, C. Regan and B. Wilson.. 284

Chloroma, myelogenous chloroma; report of case with necropsy; N. C. Foot and G. Jones.. 379

PAGE

Colloidal gold reaction in acute poliomyelitis; J. C. Regan, A. Litvak and C. Regan........ 76

Colostrum, importance of colostrum to new-born infant; A. Kuttner and B. Ratner........ 413

Cretinism, value of basal metabolism in diagnosis and treatment of; F. B. Talbot and M. E. Moriarty........ 185

Cyst, cerebral, in infant; H. G. Jacobi........ 435

Davidsohn, H., and Hymanson, A.: Saliva of the nursling........ 302

Dembo, L. H., McConnell, G. ,and Toomey, J. A.: Acute hemorrhagic encephalitis; report of case following scarlet fever........ 98

Diarrhea, bacteriologic study of acute diarrheas in young children; M. Wollstein........ 310

Diphtheria, characteristics of spinal fluid in postdiphtheric paralysis; J. C. Regan, C. Regan and B. Wilson........ 284
  comparison of diphtheria immunity in mother and in new-born; H. O. Ruh and J. E. McClelland........ 59
  Schick test performed on more than 150,000 children in public and parochial schools in New York; A. Zingher........ 392

Dunn, H. L, and Dunn, L.: Statistical analysis of causes of palpable lymph glands in new-born........ 319

Dunn, L., and Dunn, H. L.: Statistical analysis of causes of palpable lymph glands in new-born........ 319

Duodenum, atresia of duodenum and right internal hernia; report of case; J. J. Morton........ 371

Dutcher, R. A., Hall, J. S., and Cavanaugh, G. W.: Effect of spray process of drying on vitamin C content of milk........ 498

Ebaugh, F. G.: Neuropsychiatric sequelae of acute epidemic encephalitis in children........ 89

Egerer-Seham, G., and Seham, M.: Psysiology of exercise in childhood; study of normal children of school age........ 1

Encephalitis, acute hemorrhagic, report of case following scarlet fever; J. A. Toomey, L. H. Dembo and G. McConnell........ 98
  neuropsychiatric sequelae of acute epidemic encephalitis in children; F. G. Ebaugh........ 89

Exercise, physiology of exercise in childhood; study of normal children of school age; M. Seham and G. Egerer-Seham........ 1

Faber, H. K.: Critique of Pirquet feeding system........ 339

Fales, H. L., and Holt, L. E.: Calcium absorption in children on diet low in fat........ 247

Fleming, G. B.: Influence of growth on basal metabolism of children.... 85

Foot, N. C., and Jones, G.: Myelogenous chloroma; report of case with necropsy........ 379

Forbes, R. P.: Congenital malaria; report of case in Colorado........ 130

Fox, H.: Treatment of flat warts by internal administration of mercury.. 55

PAGE

Gamble, J. L., and Ross, G. S.: Studies of tetany; effect of ingestion of hydrochloric acid producing substances on acid-base metabolism of infant and probable manner of their action in treatment of tetany.... 470
  —Ross, G. S., and Tisdall, F. F.: Studies of tetany; effect of calcium chlorid ingestion on acid-base metabolism of infants.............. 455

Givens, M. H., and Howe, M. G.: Chemical studies of blood of mother and fetus 63

Gordon, J. K., and Brown, E. W.: Types of organism found in series of tuberculous children... 234

Halbertsma, T.: Mongolism in one of twins and etiology of mongolism... 350

Hall, J. S., Cavanaugh, G. W., and Dutcher, R. A.: Effect of spray process of drying on vitamin C content of milk............................ 498

Hernia, right internal hernia and atresia of duodenum; J. J. Morton....... 371

Hill, L. W.: Review of literature on blood and blood diseases of infants and children for the last 4 years (1918-1921)...................... 168
  —Hunt, E. F., and Brown, E. W.: Bacteriology of urine in acute nephritis in children.. 198

Hoag, L. A.: Malignant hypernephroma in children...................... 441

Holt, L. E., Jr.: Lead poisoning in infancy............................ 229

Holt, L. E., and Fales, H. L.: Calcium absorption in children on diet low in fat.. 247

Howe, M. G., and Givens, M. H.: Chemical studies of blood of mother and fetus.. 63

Hunt, E. F., Brown, E. W., and Hill, L. W.: Bacteriology of urine in acute nephritis in children 198

Hymanson, A., and Davidsohn, H.: Saliva of the nursling............... 302

Hypernephroma, malignant, in children; L. A. Hoag..................... 441

Idiocy, mongolism in one of twins and etiology of mongolism; T. Halbertsma 350

Infant feeding, critique of Pirquet feeding system, with special reference to its underlying principles; H. K. Faber......................... 339
  new-born, importance of colostrum to new-born infant; A. Kuttner and B. Ratner... 413
  new-born, statistical analysis of causes of palpable lymph glands in new-born; L. Dunn and H. L. Dunn.................................... 319
  new-born, transfusion through umbilical vein in hemorrhage of new-born; report of case; J. B. Sidbury.................................. 290
  premature, oxygen therapy in premature babies with anoxemia; H. Bakwin 157

Jacobi, H. G.: Case of cerebral cyst in infant......................... 435

Jones, G., and Foot, N. C.: Myelogenous chloroma; report of case with necropsy 379

Kidney, polycystic disease of kidneys; report of case in infant; A. Tow.... 222

Kuttner, A., and Ratner, B.: Importance of colostrum to new-born infant.. 413

Lead poisoning in infancy; L. E. Holt, Jr............................. 229

506

PAGE

Litvak, A., Regan, C., and Regan, J. C.: Colloidal gold reaction in acute poliomyelitis 76

Lymph glands, statistical analysis of causes of palpable lymph glands in new-born; L. Dunn and H. L. Dunn.... 319

McClelland, J. E., and Ruh, H. O.: Comparison of diphtheria immunity in mother and in new-born.... 59

McConnell, G., Toomey, J. A., and Dembo, L. H.: Acute hemorrhagic encephalitis; report of case following scarlet fever.... 98

McLean, S., and Rulison, R. H.: Treatment of vascular nevi with radium.. 359

Malaria, congenital malaria, report of case in Colorado; R. P. Forbes.... 130

Metabolism, basal, influence of growth on, of children; G. B. Fleming.... 85
  basal, value of, in diagnosis and treatment of cretinism; F. B. Talbot and M. E. Moriarty.... 185

Milk, effect of spray process of drying on vitamin C content of milk; preliminary report; G. W. Cavanaugh, R. A. Dutcher and J. S. Hall.. 498
  excretion of foreign protein in human milk; H. C. Stuart.... 135

Morbidity, causes of absence in boys' school; C. H. Sanford.... 297

Morgan, E. A.: Ulcerative stomatitis and its treatment by intravenous injection of arsenic.... 354

Moriarty, M. E., and Talbot, F. B.: Value of basal metabolism in diagnosis and treatment of cretinism.... 185

Morton, J. J.: Atresia of duodenum and right internal hernia.... 371

Nephritis, bacteriology of urine in acute nephritis in children; L. W. Hill, E. F. Hunt and E. W. Brown.... 198

Nevi, treatment of vascular nevi with radium; R. H. Rulison and S. McLean 359

Oxygen therapy in premature babies with anoxemia; H. Bakwin.... 157

Paralysis, characteristics of cerebrospinal fluid in postdiphtheric paralysis; J. C. Regan, C. Regan and B. Wilson.... 284

Pirquet feeding system, with special reference to its underlying principles; H. K. Faber.... 339

Poliomyelitis, colloidal gold reaction in; J. C. Regan, A. Litvak and C. Regan.... 76

Protein, excretion of foreign protein in human milk; H. C. Stuart.... 135

Radium treatment of vascular nevi; R. H. Rulison and S. McLean.... 359

Ratner, B., and Kuttner, A.: Importance of colostrum to new-born infant 413

Regan, C., Regan, J. C., and Litvak, A.: Colloidal gold reaction in acute poliomyelitis 76
  —Wilson, B., and Regan, J. C.: Characteristics of cerebrospinal fluid in postdiphtheric paralysis.... 284

Regan, J. C., Litvak, A., and Regan, C.: Colloidal gold reaction in acute poliomyelitis 76
  —Regan, C., and Wilson, B.: Characteristics of cerebrospinal fluid in postdiphtheric paralysis 284

PAGE

Robertson, B., and Boyd, G.: Toxemia of severe superficial burns in children 163

Ross, G. S., and Gamble, J. L.: Studies of tetany; effect of ingestion of hydrochloric acid producing substances on acid-base metabolism of infant and probable manner of their action in treatment of tetany.. 470

—Tisdall, F. F., and Gamble, J. L.: Studies of tetany; effect of calcium chlorid ingestion on acid-base metabolism of infants.......... 455

Ruh, H. O., and McClelland, J. E.: Comparison of diphtheria immunity in mother and in new-born.......... 59

Rulison, R. H., and McLean, S.: Treatment of vascular nevi with radium.. 359

Saliva of the nursling; A. Hymanson and H. Davidsohn.......... 302

Sanford, C. H.: Causes of absence in boys' school.......... 297

Sansby, J. M., and Siperstein, D. M.: Intraperitoneal transfusion with citrated blood; an experimental study.......... 107

Schools, causes of absence in boys' school; C. H. Sanford.......... 297

Seham, M., and Egerer-Seham, G.: Physiology of exercise in childhood; study of normal children of school age.......... 61

Sidbury, J. B.: Transfusion through umbilical vein in hemorrhage of new-born; report of case.......... 290

Siperstein, D. M.: Intraperitoneal transfusion with citrated blood; a clinical study 202

—and Sansby, J. M.: Intraperitoneal transfusion with citrated blood; an experimental study.......... 107

Stomatitis, ulcerative, treatment by intravenous injection of arsenic; E. A. Morgan 354

Stuart, H. C.: Excretion of foreign protein in human milk.......... 135

Talbot, F. B., and Moriarty, M. E.: Value of basal metabolism in diagnosis and treatment of cretinism.......... 185

Taylor, B.: Celiac disease.......... 46

Tetany, studies of tetany; effect of calcium chlorid ingestion on acid-base metabolism of infants; J. L. Gamble, G. S. Ross and F. F. Tisdall... 455

studies of tetany; effect of ingestion of hydrochloric acid producing substances on acid-base metabolism of infant and probable manner of their action in treatment of tetany; J. L. Gamble and G. S. Ross.... 470

Tisdall, F. F., Gamble, J. L., and Ross, G. S.: Studies of tetany; effect of calcium chlorid ingestion on acid-base metabolism of infants.... 455

Toomey, J. A., Dembo, L. H., and McConnell, G.: Acute hemorrhagic encephalitis; report of case following scarlet fever.......... 98

Tow, A.: Polycystic disease of kidneys; report of case in infant.......... 222

Tuberculosis, types of organism found in series of tuberculous children; J. K. Gordon and E. W. Brown.......... 234

Twins, mongolism in one of twins and etiology of mongolism; T. Halbertsma 350

Urine, bacteriology of urine in acute nephritis in children; L. W. Hill, E. F. Hunt and E. W. Brown.......... 198

PAGE

Vitamin, effect of spray process of drying on vitamin C content of milk; preliminary report; G. W. Cavanaugh, R. A. Dutcher and J. S. Hall.. 498

Warts, treatment of flat warts by internal administration of mercury; H. Fox 55

Wilson, B., Regan, J. C., and Regan, C.: Characteristics of cerebrospinal fluid in postdiphtheric paralysis.......... 284

Wollstein, M.: Bacteriologic study of acute diarrheas in young children... 310
—and Bartlett, F. H.: Brain tumors in young children; clinical and pathologic study 257

Zingher, A.: Schick test performed on more than 150,000 children in public and parochial schools in New York (Manhattan and the Bronx).... 392

From the Laboratory

of

Mellin's Food Company

Analysis of Mellin's Food

Fat		.16
Proteins		10.35
Maltose	58.88	
Dextrins	20.69	
Soluble Carbohydrates		79.57
Salts		4.30
Water		5.62
		100.00

Weight of Mellin's Food

1 level tablespoonful	=	105	grains or	6.805	grams
1 ounce (by volume)	=	203	" "	13.156	"

Caloric Value of Mellin's Food

1 level tablespoonful	=	25.18	Calories
1 ounce (by volume)	=	48.68	"
1 ounce (avoir.)	=	105.00	"

Mellin's Food is offered to the Medical Profession as a modifier of milk for the feeding of infants deprived of their natural nourishment, and its use as a milk modifier is consistent with the evidence accumulated since the beginning of the study of the science of infant feeding.

Prescribe Protolac Diet With *Dryco*

Infantile diarrhoeas during the summer season should be controlled by dietetic, not drug, measures.

DRYCO, dried milk, free from harmful bacteria, its casein in colloidal form, its fat readily assimilable, is the best nutrient for such purposes.

In fermentative diarrhoea, use a non-fermentative or protein diet, the best of which is PROTOLAC (calcium caseinate) in fat-free milk.

In putrefactive diarrhoea, in infants over six months old, use carbohydrate diet, barley gruel only for 24-48 hours, then gruel to which ***DRYCO*** is added in slowly increasing quantities, to supply Caloric requirement.

Send for Samples, Literature, Directions, Feeding Table, also Booklet, "The Doctor's Rubaiyat."

THE DRY MILK COMPANY

15-21 Park Row - - - - New York, N. Y.

"An International Institution for the Study and Production of Pure Milk Products"

B. B. CULTURE

A lactic culture of more than ordinary ability is required by the pediatrician. His work demands a culture of maximum viability; delay in action may be fatal. The importance of a pure culture, which is incapable of sensitization or other harm, whatever the dosage, cannot be over-emphasized.

The full validity of a culture while *important* to an adult, is *vital* to a child.

It is our feeling that, once you have used B. B. CULTURE in your work, you will continue its employment.

B. B. CULTURE LABORATORY
YONKERS NEW YORK

WANTED

BACK ISSUES

OF

AMERICAN JOURNAL DISEASES OF CHILDREN

25 cents each will be paid for any of the following copies returned in good condition: 1911: January, February, March, April, May, June; 1912: May; 1916: December; 1920: February; 1922: April. Send to

AMERICAN MEDICAL ASSOCIATION

535 N. Dearborn St., Chicago, Ill.

Valuable
in the
Infant
and
Child
Dietary

KNOX
SPARKLING
GELATINE

The Standard for Purity
and Strength

IN addition to the family size package, Knox Sparkling Gelatine is put up in 1 and 5 pound cartons for hospital use. A trial package at 80c the pound will be sent on request.

For Infant Feeding

KNOX Sparkling Gelatine is valuable in infant feeding because of its colloidal action in emulsifying the milk curd and thus facilitating digestion.

For infants from three weeks to six months old soften ½ teaspoonful of Knox Sparkling Gelatine in one ounce of milk from the day's formulae. Then add one ounce of *hot* milk from the day's formulae and stir until thoroughly dissolved. Add this solution to the full quantity of daily formulae, stirring until thoroughly mixed.

For infants from six months old up, use one teaspoonful of Knox Sparkling Gelatine.

For Growing Children

Knox Sparkling Gelatine contains 5.9% of the growth promoting amino-acid Lysine—and is highly beneficial for growing children. It combines with milk, eggs, vegetables, and fruits in making many attractive desserts and salads.

CHARLES B. KNOX GELATINE CO.
407 Knox Ave. . . Johnstown, N. Y.

Consider—

Your Reception Room Table

Is it overflowing with magazines that are several months old—that have little appeal to those who wait for you? The reading matter in your office should be of vital concern. Your reception room table can be a powerful influence in health matters. This is housecleaning time. Why not get rid of meaningless reading material and put

HYGEIA The Magazine With a Mission In Your Office

HYGEIA, with a wealth of health news and information, elaborately illustrated, full of interest to adult or child, solves the problem of timely reading matter for it will come direct to the office every month. It brings a really helpful message to all who read it. Every day more letters are received from physicians who are enthusiastic over the place HYGEIA will fill in bringing better understanding between physician and layman, in convincing the public of the important rôle of scientific medicine not only in acquiring health but in keeping health as well.

Facts You Have Long Wanted to Explain

As one physician has said, "*HYGEIA will explain the very things I have always wanted to explain to my patients, but never had the time or opportunity.*"

Of special interest to pediatricians are two practical articles for mothers in the June issue of HYGEIA. Victor C. Vaughan points out the causes of summer diarrhea in infants and Julius H. Hess gives many rules for the daily routine of the nursing mother and infant. Subsequent issues will contain a study of the basal metabolism rate in which Francis G. Benedict shows why a child is always hungry, and suggestions for occupational therapy for handicapped children by Nathaniel Allison.

Probably many other subjects will directly concern health conditions in your own community, directly explain in an impersonal way to those who wait in your office facts that you have long wanted to explain. In the largest, most helpful sense HYGEIA will live up to its sub-title, *"A Journal of Individual and Community Health."*

Your reception room table needs HYGEIA, the people who wait in your reception room need HYGEIA, you need the better understanding and cooperation that will result from having HYGEIA read in your office.

AMERICAN MEDICAL ASSOCIATION
535 N. Dearborn St., Chicago, Ill.

Please send HYGEIA for one year to my Reception Room Table at

.... (Street)
....(City and State)
I enclose $3..(Name)

MERRELL-SOULE
Special
POWDERED MILK
PRODUCTS
for Infants *and* Invalids

Fermentative Diarrhoea

"There can be but little doubt that Fermentative Diarrhoea in infants yields best to Protein Milk of high acidity in which the Lactic Acid Organisms are living and active."

—a statement made in substance by many pediatricians who have used Merrell-Soule Powdered Protein Milk.

MERRELL-SOULE POWDERED PROTEIN MILK

Analysis (Dry)		Reliquified 11 parts water and 1 part powder. (Approximating Finklestein's Formula)	
Protein	38%	Protein	3.16
Butterfat	27%	Butterfat	2.25
Lactose	24%	Lactose	2.00
Ash	5%	Ash	.42
Free Lactic Acid	3%	Free Lactic Acid	.25
Moisture	3%	Water	91.92

MERRELL-SOULE POWDERED PROTEIN MILK is a scientifically prepared protein milk from which the water is removed The full nutritive and therapeutic value of the original protein milk is retained in the powder, which will keep for months. Other pertinent facts relating to Merrell-Soule Powdered Protein Milk are:

1. It approximates Finklestein's Eiweissmilch formula differing in that
2. It is not boiled and the living lactic acid organisms are still present—
3. It is free from pathogenic bacteria—
4. It is held in fine suspension, flowing freely through the nipple—
5. It is easily prepared (requiring merely its addition to water) which insures the carrying out of the doctor's directions.

Reprints of published reports and samples are gladly sent.

MERRELL-SOULE COMPANY
Syracuse, N. Y.

601 Elm Street, Dallas, Texas
Luman R. Wing & Co.
326 W. Madison Street, Chicago, Ill.

A DISPLAY OF GOOD JUDGMENT

When a Mother selects Burkland Perfect Fitting underwear she is assured of quality and well made garments that will last and give comfort to her children. Only the finest Australian Worsted (wool) and Combed Peeler Cotton are used to make our garments and each one is sterilized and inspected before it leaves the factory.

"THE Burkland"
PERFECT FITTING

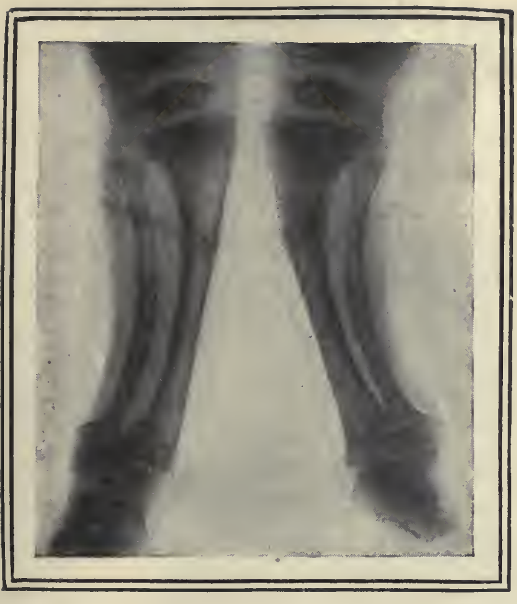
Complete Line for Infants and Children

Binder
Band
Sleeper
Single Breasted Shirt
Double Breasted Shirt
Drawers
Bloomers
Princess Slip (Gertrude)
Union Suits

BURKLAND KNITTING WORKS, Inc.

2341 Wabansia Avenue

CHICAGO - ILLINOIS



RICKETS

A Dyscrasia of Calcium and Phosphorus Metabolism

Radiogram: (Child, age 4 years.) The zones of proliferation are much wider than normal and not clearly defined owing to the irregular and imperfect assimilation of calcic phosphate at the epiphyses and diaphyses. The uneven ossification involves also the shafts of the long bones, which are almost cystic in places leading to greenstick fractures in both tibias. (Bythell and Barclay—X-Ray Diagnosis—Oxford Medical Publication.)

Therapeutic Indication: The reorganization of calcium and phosphorus metabolism to effect a normal assimilation and utilization of calcic phosphate.

Ultra-Violet Radiation:

1. Increases calcium [1]
2. Increases phosphorus [2]
3. "Fixes" calcic phosphate [3]
4. Accelerates mineral metabolism [4]
5. Corrects rickety dyscrasias [5]

It does all these things with clinical promptness and effectiveness. "Ultra-Violet Radiation in Rickets,"* a study compiled by the Biophysical Research Dept. of the Victor X-Ray Corporation, outlines the studies that have heralded this newer therapy of Rickets.

REFERENCES

1. John Howland and Benjamin Kramer: Calcium and Phosphorus in the Serum in Relation to Rickets. American Journal of Diseases of Children, August, 1921.
2. Alfred F. Hess, Margaret B. Gutman: The Cure of Infantile Rickets by Sunlight Accompanied by an Increase in the Inorganic Phosphate of the Blood, Journal of the A. M. A., January, 1922.
3. Frederick F. Tisdall: The Effects of Ultraviolet Rays on the Calcium and Inorganic Phosphate Content of the Blood Serum of Rachitic Infants. Research Laboratories of the Hospital for Sick Children, Toronto, Canada. May, 1922.
4. G. E. Powers, E. A. Park, P. G. Shipley, E. V. McCollum, and Nina Simmonds: The Prevention of the Development of Rickets in Rats by Sunlight. Studies on Experimental Rickets: XIV., Journal of the American Medical Association, January, 1922.
5. Alfred F. Hess and Lester J. Unger: The Cure of Infantile Rickets by Sunlight. Preliminary Report. The Journal of the American Medical Association, July, 1921.

**A reprint of "Ultra-Violet Radiation in Rickets" will be sent on request.*

VICTOR X-RAY CORPORATION, Jackson Blvd. at Robey St., Chicago

Sales Offices and Service Stations in All Principal Cities

VICTOR

A New Arsenobenzol Compound—for Intramuscular Injection

Desirable for the treatment of syphilis in young children, pregnant women, obese patients and others with small or inaccessible veins.

In general, useful when for any reason it is difficult or undesirable to give the trypanocidal arsenicals intravenously.

Also recommended (by Doble and others) for non-syphilitic cases, among them malaria, and other conditions.

Closely related in its chemical structure to Neoarsphenamine.

The following dosages are available in ampules: Gm. 0.2, 0.3, 0.4 and 0.6. Descriptive leaflet (C347) sent on request.

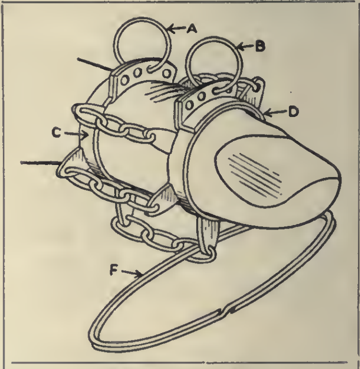
Your dealer has **Sulpharsphenamine** or can readily procure it.

THE DERMATOLOGICAL RESEARCH LABORATORIES
1720-1726 Lombard St., Philadelphia

THE ABBOTT LABORATORIES
Executive Offices, Chicago, Ill.
New York Seattle San Francisco

Break the Thumb-Sucking Habit

DR. THOMPSON'S
ANTI THUMB-SUCKING RINGS



Patent Applied For

TWO little silver rings linked with silver chains so constructed as to break the suction, thereby correcting the habit in a simple humane manner.

The rings C and D with their flexible connections scarcely interfere with the normal use of the thumb or finger. There is no discomfort, no danger, and the device is kept clean by using a brush and water without removing.

As these rings do not interfere with the child's normal activities, they can be left on until the habit has been permanently broken. It will positively cure every case if instructions are followed. Interesting brochure describing in detail the evils of this most pernicious habit of childhood, and results from use of this new device will be sent to any physician on request.

Sterling Silver Retail $3.00 Solid Gold $12.00

***The* ANTI THUMB-SUCKING RING CO.**
1601a Marshall Field Annex Building
CHICAGO - - - U. S. A.

Hoos' Albumin Milk

Protein Milk—Casein Milk—Eiweiss
Milch in powder form

KEEP IN A COOL PLACE
Contents ½ Dozen—each box containing 3 ounces (by weight)—
Package not to be broken.
Good up to 6 Months from date
HOOS' ALBUMIN MILK
CASEIN MILK—PROTEIN MILK—EIWEISS MILCH IN POWDER FORM
An Unsurpassed Modification of Milk
LOUIS HOOS--Scientific Milk Products--CHICAGO
Analysis upon dilution with water; Proteins 3.% Fat 2.5 Milk sugar 1.5 Salts .4 plus lactic ac.
PRICE $2.50

Package of six 3-oz. Cartons $2.50

Conforms to the original formula, hence contains buttermilk. Converted into powder form at a moderate degree of heat.

Analysis upon dilution with water
Proteins 3%, fat 2.5%, milk sugar 1.5%, salts .4%, plus lactic acid.

Its continued use since 1912 by leading Pediatrists speaks for itself

Literature and samples on request

Louis Hoos
Scientific Milk Products
5232 Kenmore Ave. - - - CHICAGO, ILL.

Maltine Malt Soup Extract

—with which the preparation of Malt Soup becomes easy and satisfactory.

Pamphlet reflecting the views of Dr. Keller and samples will be sent to physicians on application.

THE MALTINE COMPANY
BROOKLYN, N. Y.

THE ALPINE SUN LAMP

A Wonderful Modality for Treating Rickets

Quartz Light Therapy has created a wide interest in the Medical Sciences—especially the recent work of the foremost universities and pediatricians in treating rickets.

The results obtained would logically make the Alpine Sun Lamp a part of your necessary equipment.

We will be pleased to send you some authoritative data upon request for booklet "P".

HANOVIA CHEMICAL & MFG. CO.
NEWARK, N. J.

Branch Offices
NEW YORK CHICAGO SAN FRANCISCO

A FOOD TO KEEP BABIES AND YOUNG CHILDREN WELL

Adapted to Mother's Milk

The importance of fat in the diet of infants

One of the nutritional principles upon which S. M. A. is founded is that the fat content in the diet of infants is of vital importance in building up their resistance.

The fat in S. M. A. resembles the fat of breast milk

S. M. A. meets the need for an artificial food which contains as high a fat content as breast milk, and whose fat is comparable not only in quantity with the fat of breast milk, but also in *physical* and *chemical* properties.

S. M. A. fat is anti-rachitic and anti-spasmophilic

S.M.A. fat, in addition, has the advantage of being markedly anti-rachitic and anti-spasmophilic. It thus marks a distinct advance in infant feeding, since it prevents the development of these two nutritional disturbances.

S. M. A. contains all the required food constituents

S.M.A. also resembles breast milk in its protein, carbohydrate, salt and water content, and, in the hands of a constantly increasing number of physicians, is producing happy, healthy, breast-fed looking infants.

If you have not had the opportunity to observe the results of feeding S. M. A. in your practice, we shall be glad to send you, free of charge, a supply sufficient to enable you to do so.

THE LABORATORY PRODUCTS CO.
1111 Swetland Building ∴ Cleveland, Ohio

Formula by permission of The Babies' Dispensary and Hospital of Cleveland

MEAD'S

MEAD'S

Dependable Products

For

Pediatrists

Infant weighing scales–capacity 36 pounds by ¼ ounces
Clinic weighing scales–capacity 105 pounds by ½ ounces

Dextri-Maltose (Dextrins and Maltose)
Casec (Calcium Caseinate)
Oat Flour
Barley Flour
Cerena (Flour Ball)
Arrowroot Flour
Dry Malt Soup Stock

Literature on request

Manufacturers of ingredients for modifying cow's milk to suit the requirements of individual babies.

The Mead Johnson Policy

Mead's Infant Diet Materials are advertised only to physicians. No feeding directions accompany trade packages. Information in regard to feeding is supplied to the mother by written instructions from her doctor, who changes the feedings from time to time to meet the nutritional requirements of the growing infant. Literature furnished only to physicians.

MEAD JOHNSON & COMPANY

Evansville, Indiana., U. S. A.

LONDON ADDRESS:
40 and 42 Lexington St.

INFANT MEAD'S DIET MATERIALS

CANADIAN ADDRESS:
163 Dufferin St., Toronto, Ont.

RJ
1
A5
v.25
cop.2

American journal of diseases
of children

Biological
& Medical
Serials

PLEASE DO NOT REMOVE
CARDS OR SLIPS FROM THIS POCKET

UNIVERSITY OF TORONTO LIBRARY

STORAGE